CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number : 073045

Trade Name : ALBUTEROL INHALATION AEROSOL

Generic Name: Albuterol Inhalation Aerosol 90mcg/actuation

Sponsor : Alpharma, U.S. Pharmaceuticals Division

Approval Date: August 19, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 073045

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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 073045

APPROVAL LETTER

ANDA 73-045

AUG 19 1997

Alpharma, U.S. Pharmaceuticals Division
Attention: Ronald Bynum
333 Cassell Drive, Suite 3500
Baltimore, MD 21224

Dear Sir:

This is in reference to your abbreviated new drug application dated December 23, 1988, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Albuterol Inhalation Aerosol, 90 mcg/Actuation.

Reference is also made to your amendments dated June 12, and 22, 1995; August 1, September 11, October 8, and November 15, 1996; January 6 and 22, May 23 and 27, July 17, and August 6, 1997.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Albuterol Inhalation Aerosol, 90 mcg/Actuation to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Ventolin® Inhalation Aerosol, 90 mcg/Actuation, of Glaxo Wellcome, Inc).

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

Roger L. Williams, M.D.
Deputy Center Director for Pharmaceutical Science
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 073045

FINAL PRINTED LABELING

A.L. LABORATORIES, INC.

ANDA #73-045

Albuterol Inhalation Aerosol 17 g

200 metered Inhalations

Final Printed Labeling

THE REFILL CANISTER IS TO BE USED WITH THE CCL INDUSTRIES LTD. ADAPTER.

USUAL DOSAGE: Use only as directed by your physician.

WARNINGS: The action of Albuterol Inhalation Aerosol may last up to six hours, and therefore it should not be used more frequently than recommended. Do not increase the number or frequency of doses without consulting your physician. If symptoms get worse, discontinue use and consult your physician immediately. Other inhaled medicines should be used only as prescribed by your physician.

Shake well before using.

Manufactured by
CCL Industries Limited
Runcorn WA7 1NU
UK

Distributed by
Barre-National Inc.
Baltimore, MD 21244
USA

12640994

Barre®

NDC 0472-1264-63

ALBUTEROL INHALATION AEROSOL *Refill*

200 Metered Inhalations

17 g

For oral inhalation with CCL Industries Ltd. Albuterol Inhalation Aerosol adapter only.

Contents: Each canister contains a microcrystalline suspension of albuterol in propellants (trichloromonofluoromethane and dichlorodifluoromethane) with oleic acid. Each actuation delivers 90 mcg of albuterol from the mouthpiece.

Attention Pharmacist: Detach patient's leaflet of instructions from package insert and dispense with inhaler.

This product contains trichloromonofluoromethane and dichlorodifluoromethane, substances which harm the environment by depleting ozone in the upper atmosphere.

CAUTION: Federal law prohibits dispensing without prescription.

See package insert for full prescribing information.

Important: Read accompanying directions carefully.

Store between 15° and 30°C (59° and 86°F). As with most inhaled medications in aerosol canisters, the therapeutic effect of this medication may decrease when the canister is cold.

Shake well before using.

Contents Under Pressure: Do not puncture. Do not use or store near heat or open flame. Exposure to temperatures above 120°F may cause bursting. Never throw container into fire or incinerator. Keep out of the reach of children.

04721 26463 6

Barre®

ALBUTEROL INHALATION AEROSOL Refill

PATIENT'S INSTRUCTIONS FOR USE

Before using your Albuterol Inhalation Aerosol, read complete instructions carefully. Children should use Albuterol Inhalation Aerosol under adult supervision, as instructed by the patient's physician.

1. SHAKE THE INHALER WELL immediately before each use. **Then remove the cap from the mouthpiece.** (See Figure 1). Should the cap be dislodged or lost, the inhaler mouthpiece should be inspected for the presence of foreign objects before each use. Make sure the canister is fully and firmly inserted into the actuator.

2. BREATHE OUT FULLY THROUGH THE MOUTH, expelling as much air from your lungs as possible. Place the mouthpiece fully into the mouth, holding the inhaler in its upright position (see Figure 1) and closing the lips around it.

3. WHILE BREATHING IN DEEPLY AND SLOWLY THROUGH THE MOUTH, FULLY DEPRESS THE TOP OF THE METAL CANISTER with your index finger. (See Figure 2).

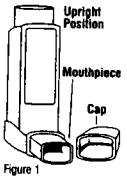


Figure 1

4. HOLD YOUR BREATH AS LONG AS POSSIBLE. Before breathing out, remove the inhaler from your mouth and release your finger from the canister.

5. Wait one minute and SHAKE the inhaler again. Repeat steps 2 through 4 for each inhalation prescribed by your physician.

6. CLEANSE THE INHALER THOROUGHLY AND FREQUENTLY. Remove the metal canister and cleanse the plastic case and cap by rinsing thoroughly in warm, running water, at least once a day. After thoroughly drying the plastic case and cap, gently replace the canister into the case with a twisting motion and replace the cap.

7. As with all aerosol medications, it is recommended to "test spray" into the air before using for the first time and in cases where the aerosol has not been used for a prolonged period of time.

8. DISCARD THE CANISTER AFTER YOU HAVE USED THE LABELED NUMBER OF INHALATIONS. The correct amount of medication in each inhalation cannot be assured after this point.

Figure 2

Carton 17 g (refill)
12640994

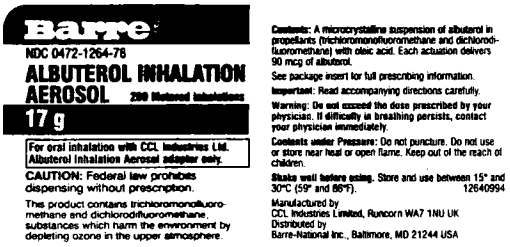
A.L. LABORATORIES, INC.

ANDA #73-045

Albuterol Inhalation Aerosol 17 g

200 metered Inhalations

Final Printed Labeling



Label 17 g

12640994

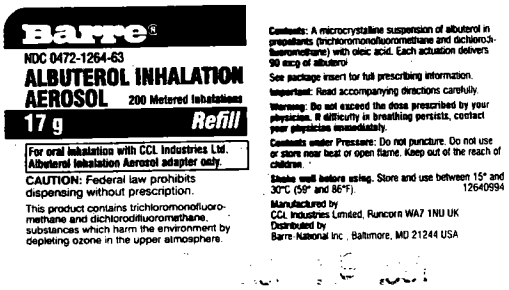
A.L. LABORATORIES, INC.

ANDA #73-045

Albuterol Inhalation Aerosol 17 g

200 metered Inhalations

Final Printed Labeling



Barre®

NDC 0472-1264-63

ALBUTEROL INHALATION AEROSOL 200 Metered Inhalations

17 g *Refill*

For oral inhalation with CCL Industries Ltd. Albuterol Inhalation Aerosol adapter only.

CAUTION: Federal law prohibits dispensing without prescription.

This product contains trichloromonofluoromethane and dichlorodifluoromethane, substances which harm the environment by depleting ozone in the upper atmosphere.

Contents: A microcrystalline suspension of albuterol in propellants (trichloromonofluoromethane and dichlorodifluoromethane) with oleic acid. Each actuation delivers 90 mcg of albuterol.

See package insert for full prescribing information.

Important: Read accompanying directions carefully.

Warning: Do not exceed the dose prescribed by your physician. If difficulty in breathing persists, contact your physician immediately.

Contents under Pressure: Do not puncture. Do not use or store near heat or open flame. Keep out of the reach of children.

Shake well before using. Store and use between 15° and 30°C (59° and 86°F). 12640994

Manufactured by
CCL Industries Limited, Runcorn WA7 1NU UK
Distributed by
Barre National Inc., Baltimore, MD 21244 USA

Label 17 g (refill)
12640994

FORM 1264 **PRODUCT INFORMATION**

ALBUTEROL INHALATION AEROSOL

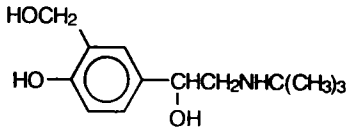
Bronchodilator Aerosol

FOR ORAL INHALATION ONLY

VC1252

WARNING: Contains trichloromonofluoromethane and dichlorodifluoromethane, substances which harm public health and environment by destroying ozone in the upper atmosphere.

DESCRIPTION: The active component of Albuterol Inhalation Aerosol is albuterol (α^1-[(*tert*-butylamino)methyl] -4-hydroxy-*m*-xylene-α,α'-diol), a relatively selective beta$_2$-adrenergic bronchodilator, having the following structural formula:



Albuterol is the official generic name in the United States. The World Health Organization recommended name for the drug is salbutamol. The molecular weight of albuterol is 239.32, and the molecular formula is $C_{13}H_{21}NO_3$. Albuterol is a white to off-white crystalline solid. It is soluble in alcohol, sparingly soluble in water, and very soluble in chloroform.

Albuterol Inhalation Aerosol is a metered-dose aerosol unit for oral inhalation. It contains a microcrystalline (95% ≤ 10μm) suspension of albuterol in propellants (trichloromonofluoromethane and dichlorodifluoromethane) with oleic acid. Each actuation delivers from the mouthpiece 90 mcg of albuterol. Each canister provides at least 200 inhalations.

CLINICAL PHARMACOLOGY: *In vitro* studies and *in vivo* pharmacologic studies have demonstrated that albuterol has a preferential effect on beta$_2$-adrenergic receptors compared with isoproterenol. While it is recognized that beta$_2$-adrenergic receptors are the predominant receptors in bronchial smooth muscle, recent data indicate that there is a population of beta$_2$-receptors in the human heart existing in a concentration between 10% and 50%. The precise function of these, however, is not yet established.

The pharmacologic effects of beta-adrenergic agonist drugs, including albuterol, are at least in part attributable to stimulation through beta-adrenergic receptors of intracellular adenyl cyclase, the enzyme that catalyzes the conversion of adenosine triphosphate (ATP) to cyclic-3',5'-adenosine monophosphate (cyclic AMP). Increased cyclic AMP levels are associated with relaxation of bronchial smooth muscle and inhibition of release of mediators of immediate hypersensitivity from cells, especially from mast cells.

Albuterol has been shown in most controlled clinical trials to have more effect on the respiratory tract, in the form of bronchial smooth muscle relaxation, than isoproterenol at comparable doses while producing fewer cardiovascular effects. Controlled clinical studies and other clinical experience have shown that inhaled albuterol, like other beta-adrenergic agonist drugs, can produce a significant cardiovascular effect in some patients, as measured by pulse rate, blood pressure, symptoms, and/or electrocardiographic changes.

Albuterol is longer acting than isoproterenol in most patients by any route of administration because it is not a substrate for the cellular uptake processes for catecholamines nor for catechol-*O*-methyl transferase.

Because of its gradual absorption from the bronchi, systemic levels of albuterol are low after inhalation of recommended doses. Studies undertaken with four subjects administered tritiated albuterol resulted in maximum plasma concentrations occurring within two to four hours. Due to the sensitivity of the assay method, the metabolic rate and half-life of elimination of albuterol in plasma could not be determined. However, urinary excretion provided data indicating that albuterol has an elimination half-life of 3.8 hours. Approximately 72% of the inhaled dose is excreted within 24 hours in the urine, and consists of 28% as unchanged drug and 44% as metabolite.

Animal studies show that albuterol does not pass the blood-brain barrier.

Recent studies in laboratory animals (minipigs, rodents, and dogs) recorded the occurrence of cardiac arrhythmias and sudden death (with histologic evidence of myocardial necrosis) when beta-agonists and methylxanthines were administered concurrently. The significance of these findings when applied to humans is currently unknown.

The effects of rising doses of albuterol and isoproterenol aerosols were studied in volunteers and asthmatic patients. Results in normal volunteers indicated that albuterol is one half to one quarter as active as isoproterenol in producing increases in heart rate. In asthmatic patients similar cardiovascular differentiation between the two drugs was also seen.

In controlled clinical trials involving adults with asthma, the onset of improvement in pulmonary function was within 15 minutes, as determined by both maximum midexpiratory flow rate (MMEF) and forced expiratory volume in one second (FEV_1). MMEF measurements also showed that near maximum improvement in pulmonary function generally occurs within 60 to 90 minutes following two inhalations of albuterol and that clinically significant improvement generally continues for three to four hours in most patients. Some patients showed a therapeutic response (defined by maintaining FEV_1 values 15% or more above baseline) that was still apparent at 6 hours. Continued effectiveness of albuterol was demonstrated over a 13-week period in these same trials.

In controlled clinical trials involving children 4 to 12 years of age, FEV_1 measurements showed that maximum improvement in pulmonary function occurs within 30 to 60 minutes. The onset of clinically significant (≥ 15%) improvement in FEV_1 was observed as soon as five minutes following 180 mcg of albuterol in 18 of 30 (60%) children in a controlled dose-ranging study. Clinically significant improvement in FEV_1 continued in the majority of patients for two hours and in 33% to 47% for four hours among 56 patients receiving inhalation aerosol in one pediatric study. In a second study, among 48 patients receiving inhalation aerosol, clinically significant improvement continued in the majority for up to one hour and in 23% to 40% for four hours. In addition, at least 50% of the patients in both studies achieved an improvement in forced expiratory flow rate between 25% and 75% of the forced vital capacity of at least 20% for two to five hours. Continued effectiveness of albuterol was demonstrated over the 12-week study period.

In other clinical studies involving both children and adults, two inhalations of albuterol aerosol taken approximately 15 minutes before exercise prevented exercise-induced bronchospasm, as demonstrated by the maintenance of FEV_1 within 80% of baseline values in the majority of patients. Two of these studies, one of which involved adults and the other children, also evaluated the duration of the prophylactic effect to repeated exercise challenges, which was evident at four hours in ***a majority of the patients*** and at six hours in approximately one third of the patients.

INDICATIONS AND USAGE: Albuterol Inhalation Aerosol is indicated for the prevention and relief of bronchospasm in patients 4 years of age and older with reversible obstructive airway disease and for the prevention of exercise-induced bronchospasm in patients 4 years of age and older.

Albuterol Inhalation Aerosol can be used with or without concomitant steroid therapy.

CONTRAINDICATIONS: Albuterol Inhalation Aerosol is contraindicated in patients with a history of hypersensitivity to any of its components.

WARNINGS: As with other inhaled beta-adrenergic agonists, albuterol inhalation aerosol can produce paradoxical bronchospasm that can be life-threatening. If it occurs, the preparation should be discontinued immediately and alternative therapy instituted.

Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs. The exact cause of death is unknown, but cardiac arrest following the unexpected development of a severe acute asthmatic crisis and subsequent hypoxia is suspected.

Immediate hypersensitivity reactions may occur after administration of albuterol inhalation aerosol, as demonstrated by rare cases of urticaria, angioedema, rash, bronchospasm, anaphylaxis, and oropharyngeal edema.

The contents of Albuterol Inhalation Aerosol are under pressure. Do not puncture. Do not use or store near heat or open flame. Exposure to temperatures above 120°F may cause bursting. Never throw container into fire or incinerator. Keep out of the reach of children.

PRECAUTIONS: General: Albuterol, as with all sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension; in patients with convulsive disorders, hyperthyroidism, or diabetes mellitus; and in patients who are unusually responsive to sympathomimetic amines.

PHARMACIST – DETACH HERE AND GIVE INSTRUCTIONS TO PATIENT. THIS LEAFLET SHOULD ACCOMPANY EACH ALBUTEROL INHALATION AEROSOL OR REFILL DISPENSED

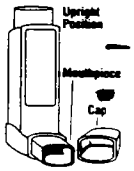
This product contains trichloromonofluoromethane and dichlorodifluoromethane, substances which harm the environment by depleting ozone in the upper atmosphere.

Patient's Instructions for Use

Before using your Albuterol Inhalation Aerosol, read complete instructions carefully.

Children should use Albuterol Inhalation Aerosol under adult supervision, as instructed by the patient's physician.

Figure 1



1. SHAKE THE INHALER WELL immediately before each use. **Then remove the cap from the mouthpiece.** (See Figure 1). Should the cap be dislodged or lost, the inhaler mouthpiece should be inspected for the presence of foreign objects before each use. Make sure the canister is fully and firmly inserted into the actuator.

2. BREATHE OUT FULLY THROUGH THE MOUTH, expelling as much air from your lungs as possible. Place the mouthpiece fully into the mouth, holding the inhaler in its upright position (See Figure 1) and closing the lips around it.

3. WHILE BREATHING IN DEEPLY AND SLOWLY THROUGH THE MOUTH, FULLY DEPRESS THE TOP OF THE METAL CANISTER with your index finger. (See Figure 2).

For Oral Inhalation Only

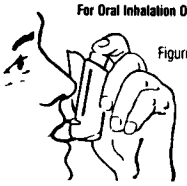


Figure 2

4. HOLD YOUR BREATH AS LONG AS POSSIBLE. Before breathing out, remove the inhaler from your mouth and release your finger from the canister.

5. Wait one minute and **SHAKE** the inhaler again. Repeat steps 2 through 4 for each inhalation prescribed by your physician.

6. CLEANSE THE INHALER THOROUGHLY AND FREQUENTLY. Remove the metal canister and cleanse the plastic case and cap by rinsing thoroughly in warm, running water, at least once a day. After thoroughly drying the plastic case and cap, gently replace the canister into the case with a twisting motion and replace the cap.

7. As with all aerosol medications, it is recommended to "test spray" into the air before using for the first time and in cases where the aerosol has not been used for a prolonged period of time.

8. DISCARD THE CANISTER AFTER YOU HAVE USED THE LABELED NUMBER OF INHALATIONS. The correct amount of medication in each inhalation cannot be assured after this point.

(continued)

1997 AUG 19

THE REFILL CANISTER IS TO BE USED WITH THE CCL INDUSTRIES LTD. ADAPTER

DOSAGE: Use only as directed by your physician.

WARNINGS: The action of Albuterol Inhalation Aerosol may last up to six hours, and therefore it should not be used more frequently than recommended. Do not increase the **number or frequency of doses without consulting your physician. If recommended dosage does not provide relief of symptoms or symptoms become worse, seek immediate medical attention. While taking Albuterol Inhalation Aerosol, other inhaled medicines should be used only as prescribed by your physician.**

Contents Under Pressure. Do not puncture. Do not use or store near heat or open flame. Exposure to temperatures above 120°F may cause bursting. Never throw container into fire or incinerator. Keep out of the reach of children.

Store between 15° and 30°C (59° and 86°F). As with most inhaled medications in aerosol canisters, the therapeutic effect of this medication may decrease when the canister is **cold. Shake well before using.**

Manufactured by
CCL Industries Limited
Runcorn WA7 1NU
UK

Distributed by
Barre-National Inc.
Baltimore, MD 21244
USA

FORM NO. 1264-P
Rev.8/96

PHARMACIST – DETACH HERE AND GIVE INSTRUCTIONS TO PATIENT. THIS LEAFLET SHOULD ACCOMPANY EACH ALBUTEROL INHALATION AEROSOL OR REFILL DISPENSED

Large doses of intravenous albuterol have been reported to aggravate pre-existing diabetes mellitus and ketoacidosis. As with other beta-agonists, inhaled and intravenous albuterol may produce significant hypokalemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects. The decrease is usually transient, not requiring supplementation.

Although there have been no reports concerning the use of Albuterol Inhalation Aerosol during labor and delivery, it has been reported that high doses of albuterol administered intravenously inhibit uterine contractions. Although this effect is extremely unlikely as a consequence of aerosol use, it should be kept in mind.

Information for Patients: The action of Albuterol Inhalation Aerosol may last up to six hours, and therefore it should not be used more frequently than recommended. Do not increase the number or frequency of doses without medical consultation. If recommended dosage does not provide relief of symptoms or symptoms become worse, seek immediate medical attention. While taking Albuterol Inhalation Aerosol, other inhaled drugs should not be used unless prescribed.

In general, the technique for administering Albuterol Inhalation Aerosol to children is similar to that for adults, since children's smaller ventilatory exchange capacity automatically provides proportionally smaller aerosol intake. Children should use Albuterol Inhalation Aerosol under adult supervision, as instructed by the patient's physician.

See illustrated **Patient's Instructions For Use.**

Drug Interactions: Other sympathomimetic aerosol bronchodilators should not be used concomitantly with albuterol. If additional adrenergic drugs are to be administered by any route, they should be used with caution to avoid deleterious cardiovascular effects.

Albuterol should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants because the action of albuterol on the vascular system may be potentiated.

Beta-receptor blocking agents and albuterol inhibit the effect of each other.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Albuterol sulfate, like other agents in its class, caused a significant dose-related increase in the incidence of benign leiomyomas of the mesovarium in a two-year study in the rat at oral doses of 2, 10, and 50 mg/kg, corresponding to 93, 463, and 2,315 times, respectively, the maximum inhalational dose for a 50 kg human. In another study this effect was blocked by the coadministration of propranolol. The relevance of these findings to humans is not known. An 18-month study in mice and a lifetime study in hamsters revealed no evidence of tumorigenicity. Studies with albuterol revealed no evidence of mutagenesis. Reproduction studies in rats revealed no evidence of impaired fertility.

Pregnancy: *Teratogenic Effects:* Pregnancy Category C: Albuterol has been shown to be teratogenic in mice when given in doses corresponding to 14 times the human dose. There are no adequate and well-controlled studies in pregnant women. Albuterol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. A reproduction study in CD-1 mice given albuterol subcutaneously (0.025, 0.25, and 2.5 mg/kg, corresponding to 1.15, 11.5, and 115 times, respectively, the maximum inhalational dose for a 50 kg human) showed cleft palate formation in 5 of 111 (4.5%) fetuses at 0.25 mg/kg and in 10 of 108 (9.3%) fetuses at 2.5 mg/kg. None was observed at 0.025 mg/kg. Cleft palate also occurred in 22 of 72 (30.5%) fetuses treated with 2.5 mg/kg isoproterenol (positive control). A reproduction study with oral albuterol in Stride Dutch rabbits revealed cranioschisis in 7 of 19 (37%) fetuses at 50 mg/kg, corresponding to 2,315 times the maximum inhalational dose for a 50 kg human.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because of the potential for tumorigenicity shown for albuterol in animal studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in pediatric patients below 4 years of age have not been established.

ADVERSE REACTIONS

The adverse reactions to albuterol are similar in nature to reactions to other sympathomimetic agents, although the incidence of certain cardiovascular effects is lower with albuterol.

A 13-week, double-blind study compared albuterol and isoproterenol aerosols in 147 asthmatic patients aged 12 years and older. The results of this study showed that the incidence of cardiovascular effects was: palpitations, fewer than 10 per 100 with albuterol and fewer than 15 per 100 with isoproterenol; tachycardia, 10 per 100 with both albuterol and isoproterenol; and increased blood pressure, fewer than 5 per 100 with both albuterol and isoproterenol. In the same study, both drugs caused tremor or nausea in fewer than 15 patients per 100, and dizziness or heartburn in fewer than 5 per 100 patients. Nervousness occurred in fewer than 10 per 100 patients receiving albuterol and in fewer than 15 per 100 patients receiving isoproterenol.

In 12-week, double-blind studies involving the use of Albuterol Inhalation Aerosol 180 mcg qid by 104 asthmatic children aged 4 to 11 years showed the following side effects:

Central Nervous System: Headache, 3 of 104 patients (3%); nervousness, lightheadedness, agitation, nightmares, hyperactivity, and aggressive behavior, each in 1%.

Gastrointestinal: Nausea and/or vomiting, 6 of 104 (6%); stomachache, 3 of 104 (3%); diarrhea in 1%.

Oropharyngeal: Throat irritation, 6 of 104 (6%); discoloration of teeth in 1%.

Respiratory: Epistaxis, 3 of 104 (3%); coughing, 2 of 104 (2%).

Musculoskeletal: Tremor and muscle cramp, each in 1%.

Rare cases of urticaria, angioedema, rash, bronchospasm, hoarseness and oropharyngeal edema have been reported after the use of inhaled albuterol.

In addition, albuterol, like other sympathomimetic agents, can cause adverse reactions such as hypertension, angina, vertigo, central nervous system stimulation, insomnia, and unusual taste.

OVERDOSAGE: Manifestations of overdosage may include seizures, anginal pain, hypertension, hypokalemia, tachycardia with rates up to 200 beats per minute, and exaggeration of the pharmacologic effects listed in ADVERSE REACTIONS.

As with all sympathomimetic aerosol medications, cardiac arrest and even death may be associated with abuse.

The oral LD_{50} in male and female rats and mice was greater than 2,000 mg/kg. The inhalational LD_{50} could not be determined.

Dialysis is not appropriate treatment for overdosage of albuterol inhalation aerosol. The judicious use of a cardioselective beta-receptor blocker, such as metoprolol tartrate, is suggested, bearing in mind the danger of inducing an asthmatic attack.

DOSAGE AND ADMINISTRATION: For treatment of acute episodes of bronchospasm or prevention of asthmatic symptoms, the usual dosage for adults and children 4 years and older is two inhalations repeated every four to six hours; in some patients, one inhalation every four hours may be sufficient. More frequent administration or a larger number of inhalations are not recommended.

The use of Albuterol Inhalation Aerosol can be continued as medically indicated to control recurring bouts of bronchospasm. During this time most patients gain optimal benefit from regular use of the inhaler. Safe usage for periods extending over several years has been documented.

If a previously effective dosage regimen fails to provide the usual relief, medical advice should be sought immediately as this is often a sign of seriously worsening asthma which would require reassessment of therapy.

Exercise-Induced Bronchospasm Prevention: The usual dosage for adults and children 4 years and older is two inhalations 15 minutes before exercise.

For treatment, see above.

HOW SUPPLIED: Albuterol Inhalation Aerosol is supplied in 17-g canisters in boxes of one with patient's instructions and an oral adaptor or as refills, without oral adaptor. Each actuation delivers 90 mcg of Albuterol from the mouthpiece. Each canister provides 200 metered inhalations.

Store at controlled room temperature 15°-30°C (59°-86°F). As with most inhaled medications in aerosol canisters, the therapeutic effect of this medication may decrease when the canister is cold.

Shake well before using.

CAUTION: Federal law prohibits dispensing without prescription.

Manufactured by
CCL Industries Limited
Runcorn WA7 1NU
UK

Distributed by
Barre-National Inc.
Baltimore, MD 21244
USA

FORM NO. 1264 Rev.8/96 VC1252

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 073045

CHEMISTRY REVIEW(S)

1. CHEMISTRY REVIEW NO. 9

2. ANDA # 73-045

3. NAME AND ADDRESS OF APPLICANT
ALPharma (previously known as A.L. Laboratories)
The Johns Hopkins Bayview Research Campus
333 Cassell Drive, Suite 3500
Baltimore, MD 21224

Name of the previous applicant/owner of the ANDA:
Generics (U.K) Ltd.
England
(Ownership transferred per OGD's letter dated 5-29-92)

4. BASIS OF SUBMISSION
Expiration of the patent covering the listed drug product, Ventolin Inhalation Aerosol.

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
None used

7. NONPROPRIETARY NAME
Albuterol Inhalation Aerosol

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:
FIRM:
Original submission: 12-28-88
Amendment: 3-6-89
ONC (Bio Data): 5-16-89
ONC (Bio Data): 6-23-89
Amendment: 8-28-89 (To submit response to NA letter dated 6-26-89.
ONC (Bio data): 3-23-90
ONC: 6-18-90
Amendment: 4-30-90
Amendment: 7-5-90 (To submit response to NA letter dated 6-26-89 and 4-23-90)
Amendment: 11-19-90 (labeling)
ONC: 11-21-90
ONC: 1-2-91 (Clinical)
Amendment: 4-26-91 (labeling)
ONC: 5-7-92
NC: 7-26-93
Major Amendment: 2-4-94 (To submit response to NA letter dated 7-21-91).
Major Amendment: 12-2-94 (Response to NA letter dated 8-11-94)
Amendment: 1-27-95
ONC: 6-12-95 (BIO)
ONC: 6-22-95 (BIO)

Major Amendment: 8-1-95 (Response to NA letter dated 5-26-95)
Minor Amendment: 2-23-96 (Response to NA letter dated 1-29-96)
3-27-96 MV Information
4-1-96 PAI Information
Minor Amendment: 5-1-96 (Response to NA letter dated 4-18-96)
ONC: 8-1-96 (Response to 7-18-96 bio letter)
Telephone amendment: 8-22-96 (submitted as a results of telecon dated 8-22-96)
8-30-96: Transfer of ownership
Telephone amendment: 9-5-96 (Response to Fax dated 8-23-96 regarding MV)
9-11-96: Big Data
9-20-96:Labeling
Telephone amendment: 9-30-96 (Response to Fax dated 9-25-96 regarding MV)
Amendment (Bio): 10-8-96 (Response to bio letter dated 9-3-96)
* Amendment (Bio): 5-23-97 (Response to bio letter dated 5-12-97)
* Amendment: 5-27-97 (Response to NA Chemistry letter dated 5-20-97)
* Telephone amendment: 7-17-97

FDA:
Acknowledgement Letter: 1-13-89
Bio NA letter: 9-19-89
NA letter (chemistry & Labeling): 6-26-89 (Reviewer - F. Fang for CR # 1)
NA letter (Chemistry & labeling): 4-23-90 (Reviewer - J.T. Piechocki for CR # 2)
Information letter (Labeling): 9-25-90
NA letter (Chemistry & Labeling): 7-12-91
Acknowledgement letter for ownership change: 5-29-92
NA letter: 8-11-94 (CR # 4)
NA letter: 5-26-95 (CR # 5)
NA letter: 1-29-96 (CR # 6)
NA letter: 4-8-96 (CR # 7)
Deficiency letter: 7-18-96 (Bio)
Deficiency letter: 9-3-96 (Bio)
FAX: 8-23-96 (MV comments)
FAX: 9-23-96 (MV Comments)
Deficiency letter (BIO): 5-12-97
NA Letter (Chemistry): 5-20-97

10. PHARMACOLOGICAL CATEGORY
Bronchodilator

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)

13. DOSAGE FORM
Inhalation Aerosol

14. POTENCY
0.09 mg/Actuation

15. CHEMICAL NAME AND STRUCTURE
Satisfactory per CR # 1

16. RECORDS AND REPORTS
N/A

17. COMMENTS
1. Referenced DMF is adequate per last review completed by M. Shaikh review dated 10-15-96. No new amendment is submitted after this review.
The supporting DMFs became per review completed by this reviewer on 10-15-96 after review of 9-13-96 amendment. Remains adequate per review completed by this reviewer on 7-10-97 after review of 2-25-97 annual update.
2. Release and stability specifications for the finished drug product remains acceptable.
3. 24 months CRT stability data for exhibit batch (lot # 6403 submitted in this amendment is adequate to grant the 2 years of expiration dating period.
4. ALPharma's amendment dated 5-27-97 is acceptable from chemistry point of view.
5. EER submitted on 1-3-96 by this reviewer became acceptable on 5-29-96. A follow-up EER need to be submitted
6. MV conducted by DDA, St. Louis, MO is Acceptable.
7. FPL - acceptable per labeling review conducted on 10-8-96 by C. Holquist.

18. CONCLUSIONS AND RECOMMENDATIONS
Approved pending acceptable EER update.

19. REVIEWER:
Mujahid L. Shaikh

DATE COMPLETED:
7-17-97

cc: ANDA 73-045
DUP File
Division File
Field Copy

7/28/97

Endorsements:
HFD-623/M.Shaikh/7-17-97
HFD-623/M.Smela/7-18-97

7/29/97

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F/T by: bc/7-21-97

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 073045

BIOEQUIVALENCE REVIEW(S)

DIV

SEP 3 1996

Albuterol Inhalation Aerosol (MDI)
90 µg/actuation
ANDA 73-045
Reviewers: Z.Z. Wahba; W.P. Adams
73045sd3.695

A.L. Laboratories
Submission Dates:
12 Jun 95
22 Jun 95
1 Aug 96

FURTHER REVIEW OF IN VITRO BIOEQUIVALENCE STUDY DATA AND RESPONSE TO A DEFICIENCY LETTER

I. BACKGROUND

The Division of Bioequivalence (DBE) *Guidance for the In Vitro Portion of Bioequivalence Requirements for Metaproterenol Sulfate and Albuterol Inhalation Aerosols (Metered Dose Inhalers)*, issued 27 Jun 89, recommends comparative data to characterize *in vitro* performance of the test product relative to that of the reference listed drug (RLD). The firm's 12 Jun 95 submission provides comparative data. A DBE review of the firm's *in vivo* and *in vitro* data, dated 17 Jul 96, included a list of deficiencies of the *in vitro* data, which was communicated to the firm in a 18 Jul 96 letter. The firm's 1 Aug 96 amendment responds to these deficiencies. For convenience, this review will include relevant *in vitro* data from the 17 Jul 96 review, along with data from the 1 Aug 96 amendment.

The firm states that test product MDI samples for both the *in vitro* and *in vivo* studies were collected from beginning, middle and end of the packaging run. From these samples, canisters to be used in the testing were randomly selected.

II. PRODUCT INFORMATION AND FORMULATION COMPARISON

DRUG DEVICE AND FORMULATION DATA SHOULD NOT BE RELEASED UNDER FOI

A. Reference listed drug and test product used in the *in vitro* and *in vivo* bio studies:

1. Reference Listed Drug

Ventolin[R] Inhalation Aerosol
90 µg/actuation
Manufacturer: Allen & Hanburys, Division of Glaxo
Lot #Z31383LS
Expiration Date: Mar 96

Nominal dose ex-valve: 0.100 mg (100 μg)
Nominal dose ex-actuator: 0.090 mg (90 μg)
Weight albuterol per canister: 27.6 mg
Number of theoretical doses based on drug content: 27.6 mg/0.100 = 276
Average shot weight: 85 mg
(Reference: ANDA Vol. A8.2, p. 627)
Number of theoretical doses based on shot weight: 20771 mg/85 mg = 244

2. Test Product
(Reference: vol. A8.2, page 690)

Albuterol Inhalation Aerosol
90 μg/actuation
Manufacturer:

Lot #6403 (ALB6403)

Theoretical Lot/Batch size:
Total units filled:
Lot size, minus rejects:
Manufacture date (filling of canisters): Jul 93
Packaging with actuator: Aug 93
Expiration Date: Jun 95
Declared Doses: 200

Can-component Specifications
(Reference: Vol. A6.1, pp. 294, 321, 352, 355)

Nominal dose ex-valve: 0.100 mg (100 μg)
(Reference: Vol. A8.1, p. 523)
Nominal dose ex-actuator: 0.090 mg (90 μg)
Weight albuterol per canister: 23.18 mg
Number of theoretical doses based on drug content:
23.2/0.100 = 232
Average shot weight: 88 mg
(Reference: Vol. A8.2, p. 626, and 1 Aug 96 amendment, 119-123)
Number of theoretical doses based on shot weight:
20000/88 = 227

B. Comparative formulations:

Composition of test and RLD products is expressed several ways:

1. Weight of ingredient per canister Table 1)
2. % weight/weight (Table 2)
3. Weight of ingredient per actuation, based on drug content and a nominal dose ex-valve of 0.100 mg (100 μg) (Table 3)
4. Weight of ingredient per actuation, based on average shot weight, and the weight of suspension in the canister (Table 4)

The most appropriate method for making formulation comparisons has not been decided. However, because the formulation is dispensed by volume valve in the test product), shot weight may be an appropriate basis upon which to adjust composition (Table 4).

Table 1
Comparative Formulations
(Weight of Ingredient per Canister)

Ingredients	Test*	Reference**	T/R
Albuterol, USP	23.18 mg	27.6 mg	0.840
Oleic Acid, NF			
Trichloromonofluoromethane,NF			
Dichlorodifluoromethane, NF			
Total mg/Canister***	20000 mg	20771 mg	0.963

* 90 μg per dose delivered to patient, approximately 10% retained on mouthpiece.

* Includes a 15.9% overage to deliver a minimum of 200 doses per canister.

** The information of the RLD was provided in NDA #18-473, Volume #8.1, Annual Report R-08, Section C, covering the period of 01 June 1984 to 31 May 1985. The RLD includes a 10% formula overage.

*** Obtained by addition of the four ingredients.

Table 2
Comparative Formulations
(% Weight/Weight; %W/W)

Ingredients	Test Product % W/W	RLD % W/W
Albuterol, USP	0.1159%	0.1329%
Oleic Acid, NF		
Trichloromonofluoromethane, NF		
Dichlorodifluoromethane, NF		
Total	100.00%	100.00%

Table 3
Comparative Formulations
(Weight of Ingredient per Actuation)
(Based on Drug Content)

Ingredients	Test*	Reference**	T/R
Albuterol, USP	100 μg	100 μg	1.00
Oleic Acid, NF			
Trichloromonofluoromethane,NF (Propellant 11)			
Dichlorodifluoromethane, NF (Propellant 12)			
Total mg/Canister***	86.21 mg	75.25 mg	1.146

* Nominal 90 μg per actuation delivered to patient, approximately 10% of dose ex-actuator retained on mouthpiece.

* Includes a 15.9% (16%) overage to deliver a minimum of 200 actuations per canister. The overage accounts for filling variability and assures that the metering chamber of the aerosol valve is completely covered during the entire 200 labeled actuations. (Reference: 1 Aug 96 amendment)

* The information of the test product was provided in Volumes A1.1, p. 93; A8.1, p. 481; and A10.1 (Biobatch Identity section)

** The information of the RLD was provided in NDA #18-473, Volume 8.1, Annual Report R-08, Section C, covering the period of 1 Jun 84 to 31 May 85.

*** Obtained by addition of the four ingredients.

Table 4
Comparative Formulations
(Weight of Ingredient per Actuation)
(Based on Average Shot Weight)

Ingredients	Test	Reference**	T/R
Albuterol, USP	102.1 μg	113.1 μg	0.903
Oleic Acid, NF			
Trichloromonofluoromethane,NF			
Dichlorodifluoromethane, NF			

Metering valves are designed to dispense volumetrically (A.J. Hickey, ed., *Pharmaceutical Inhalation Aerosol Technology*, Dekker, 1992, p. 173). The number of doses per canister is thus a function, in part, of the volume of the metering chamber, which affects the shot weight, and the weight of total suspension in the canister. Hence, formulation comparison based on average shot weights (Table 4) seems appropriate. This comparison indicates that:

> TEST PRODUCT IS WITHIN -10% AND +6% OF RLD ON VARIOUS INACTIVE INGREDIENTS,

which exceeds the 5% Q_2 limit recommended by the 17 Nov 94 OGD *Interim Inactive Ingredients Policy for* filing an ANDA. However, the Policy indicates that Q_2 may differ under certain circumstances, provided an *in vivo* study is conducted. It is noted that this ANDA was filed 23 Dec 88, preceding the Policy.

III. PARTICLE SIZE DISTRIBUTION BY CASCADE IMPACTOR

The Division of Bioequivalence guidance (June 27, 1989) recommends particle size determination by at least two different methods, including the pivotal cascade impactor data. The firm determined the particle size by using the following methods: cascade impactor, laser diffraction, and twin impinger.

Atomizing chamber: USP 23 metal throat
Flow rate:
Number of actuations per canister: 25

Note: USP 23 <601> specifies that the flow rate through the cascade impactor be within 2% of that specified by the manufacturer (28.3 L/min for the CI). Volume A7.1, p. 179 provides validation data for CI studies conducted at The firm concludes (1 Aug 96 amendment, Response 2) that differences in flow rate over this range had no significant effect on particle size results. In the reviewer's opinion, this conclusion is not justified in view of excessive variability. However, a flow rate can be accepted in view of the comparative nature of the CI data.

Note: The cascade impactor test product data reported in Volume A8.2, p. 565, contains an apparent typographical error for canister 2, stage 3, end sector (34747).

The cascade impactor apparatus (USP 23, Chapter 601) is used to determine the following:

(a) Total mass of drug released from the inhalation aerosol.
(b) Quantity of drug collected at each location of the cascade impactor device.
(c) Mass median aerodynamic diameter (MMAD; the diameter above and below which 50% of the mass of the drug reside).
(d) Geometric standard deviation (GSD).
(e) Respirable dose and respirable fraction.

Assay Method

Cascade impactor data for three canisters of test product and three canisters for RLD at BME are given on pp. 565 and 567, vol. A8.2.

UNACCEPTABLE CASCADE IMPACTOR DATA

CASCADE IMPACTOR DATA ARE PIVOTAL *IN VITRO* COMPARISONS AS ISSUED ON 27 JUN 89 IN THE DBE IN VITRO GUIDANCE. FOR THE FIVE REASONS LISTED BELOW, THE REVIEWERS BELIEVE THAT NO CONCLUSIONS CAN BE DRAWN FROM THE CASCADE IMPACTOR DATA PROVIDED BY THE FIRM IN ITS 12 JUN 95 AND 1 AUG 96 SUBMISSIONS. A MEETING WITH THE FIRM IS REQUESTED.

Cascade impactor data for drug deposited on each of the (Vol. A8.2, pp. 565, 567) and on the actuator and induction port (USP metal throat; 1 Aug 96 amendment, pp. 2-3) are provided for beginning, middle and end of three canisters each of test product and RLD. These data suggest a significant analytical problem. The bases for this conclusion are the following observations:

1. High inter- and intracanister variability in drug deposition on a number of cascade impactor (bioequivalence study batches). Data are provided in Volume A8.2, pp. 565, 567. The cause appears to be analytical, and is observed at stages with high drug deposition (e.g., stage 5, test product) and with low deposition (stages 0 - 2).

2. High intercanister variability in MMAD of validation data. The cascade impactor validation report (Volume A7.1, p. 10), reveals at flow rate, a MMAD range of 2.29 to 3.30 microns, and at flow rate, a MMAD range of 2.00 to 4.00.

   Note: This validation method is the same method used to generate the comparative cascade impactor data supporting the *in vitro* bioequivalence data (1 Aug 96 amendment).

   Note: Neither raw data for the validation studies (Volume A7.1, p. 10), nor geometric standard deviations (GSD's) were reported for these studies. The cause of the variability thus cannot be assessed.

   Note: The reviewers disagree with the firm's assertion (1 Aug 96 amendment, p. 3) that the validation data conducted at and suggest little difference in drug deposition. The observed excessive variability in MMAD at each flow rate prohibits any conclusion of absence of flow rate differences.

3. High inter- and intracanister variability in GSD's of test product, and high inter-canister variability in GSD's of reference listed drug (Volume A8.2, pp. 565, 567; Table 6 of this review). These data are suggestive of substantially different slopes of the log probability plots, implying different distribution profiles.

4. Test/reference product ratios of mean respirable dose values at beginning, middle and end canister sectors range from 1.04 to 1.60, and for respirable fraction, from 0.904 to 1.34, based on drug < 5.8 microns (Table 7 of this review). These results are suggestive of analytical problems.

5. Validation of the assay used to quantify drug on each stage of the cascade impactor was not submitted. The firm was requested (letter of 18 Jul 96) to provide dated laboratory worksheets. These sheets, which were not submitted, would have assisted in evaluation of the firm's data.

Table 5
Total Drug Recovery*
(mg per 25 actuations)

Shot #	Test Product (Batch #6403)			Reference Product (Batch #Z31383LS)		
	Mean	Range	%CV	Mean	Range	%CV
Start (n = 3) 6-30	2.83	2.48-3.27	14.2	2.57	2.52-2.60	1.62
Middle (n = 3) 91-115	2.92	2.58-3.23	11.2	2.60	2.43-2.70	5.79
End (n = 3) 176-200	2.94	2.23-3.36	21.1	2.46	2.43-2.50	1.43

* Total mass of drug recovered from stages and filter, plus drug in induction port (USP metal throat) plus drug in actuator. Data from Column C, pp. 2-3, 1 Aug 96 amendment

Comment:

Intercanister %CV's for test product are higher than for RLD at beginning,

middle and end canister sectors. This difference suggests a difference between products, although no conclusions can be made in the absence of an acceptable cascade impactor method.

MATERIAL BALANCE CALCULATION

The firm was requested to calculate material balance as defined in USP <601>, p. 1764. The firm's response (1 Aug 96 amendment, response 5, claims that the calculation is theoretical, based on the manufacturing formula. This is incorrect. USP specifically outlines this calculation, based on actual shot weight and measurement of drug concentration in the batch under consideration (assay of total drug in canister, and weight of total contents). Material balance enables a true estimate of drug recovered in the cascade impactor experiment relative to expected delivery. The firm's calculation, reported as "% mass balance" (1 Aug 96 amendment, Comment # 1 section, pp. 2-3), is NOT CORRECT. Actual expected drug delivery for test and RLD products was not determined. In addition, it is inappropriate for the firm to assume that the RLD has the same drug concentration in the suspension as does the test product (Reference: Table 1 of this review).

Table 6
Mass Median Aerodynamic Diameter (MMAD)
(microns)

	A.L. Laboratories (Lot 6403) MMAD, microns (GSD)				Ventolin (Lot Z31383LS) MMAD, microns (GSD)			
Spray #	Can 1	Can 2	Can 3	Mean	Can 1	Can 2	Can 3	Mean
6-30	2.4 (1.70)	3.0 (1.90)	2.45 (2.55)	2.62	2.25 (2.12)	2.3 (1.50)	2.4 (1.55)	2.32
91-115	2.4 (1.63)	2.5 (2.19)	2.75 (2.52)	2.55	2.25 (2.16)	2.35 (1.51)	2.35 (1.52)	2.32
176-200	2.65 (1.86)	2.5 (2.68)	2.6 (2.61)	1.98	2.4 (2.22)	2.3 (1.50)	2.4 (1.50)	2.37
Mean	2.48	2.67	2.60	2.58*	2.3	2.32	2.38	2.33*

MMAD: mass median aerodynamic diameter in microns
GSD: geometric standard deviation
*: grand means are underlined
Each MMAD and associated GSD represents the data of one cascade impactor experiment.

Table 7
Cascade Impactor: Respirable Dose and Respirable Fraction: Drug < 5.8 Microns

Shot #	"Respirable Dose" (μg/actuation)		
	Test (Lot 6403)	Reference (Lot Z31383LS)	T/R
6-30	35.8(17.2)	34.5(10.9)	1.04
91-115	44.8(15.6)	32.0(7.02)	1.40
176-200	48.2(17.8)	30.2(7.66)	1.60
OVERALL	42.9	32.2	1.33
Shot #	"Respirable Fraction"		
6-30	0.337(0.116)	0.373(0.124)	0.904
91-115	0.407(0.109)	0.332(0.070)	1.26
176-200	0.436(0.079)	0.326(0.085)	1.34
OVERALL	0.393	0.344	1.14

Data are given as mean (SD) of three experiments (i.e., three canisters).

Table 8
Cascade Impactor: Respirable Dose and Respirable Fraction: Drug < 4.7 Microns

Shot #	"Respirable Dose" (μg/actuation)		
	Test (Lot 6403)	Reference (Lot Z31383LS)	T/R
6-30	31.6(14.2)	33.0(10.1)	0.958
91-115	38.9(13.3)	30.7(6.21)	1.27
176-200	42.0(14.8)	28.7(6.54)	1.46
OVERALL	37.5	30.8	1.22
Shot #	"Respirable Fraction"		
6-30	0.299(0.094)	0.357(0.115)	0.838
91-115	0.353(0.093)	0.320(0.064)	1.10
176-200	0.382(0.062)	0.309(0.073)	1.24
OVERALL	0.345	0.329	1.05

Data are given as mean (SD) of three experiments (i.e., three canisters).

IV. PARTICLE SIZE DISTRIBUTION BY LASER DIFFRACTION

contract manufacturer of the test product, developed a nonstandard method for sizing particles from the aerosol cloud. The method involves heating the MDI prior to actuation. The firm is inconsistent regarding the temperature - the 12 Jun 95 amendment (Vol. A8.2, p. 571, states that the canister is heated to , the 1 Aug 96 amendment, p. 136, states that the canister is heated to . The method uses a downpipe (sampling tube) heated to about propellant. The MDI is actuated every until the test is finished. The method is intended to provide a measure of drug particle size, rather than aerosol droplet size. The method is nonstandard, and is not a 'regulatory method' in the firm's ANDA.

Laser Diffraction

Sampling tube specifications are:

Diameter at base of tube:
Diameter at top of tube:

Length of tube:
Distance from the beam:
Distance above the beam:
Downpipe temperature:
MDI canister temperature:

Size determination was made on three canisters at beginning, middle and end sectors. Specific actuation (station) numbers were not provided. Volume distribution [D(v,0.5)] and a measure of dispersion, span {[D(v,0.9) - D(v,0.1)]/D(v,0.5)}, are listed in Table 9.

Table 9
Particle Size Delivered from
the Actuator (Mouthpiece) Laser[1,2]
(in microns)

Shot	Test Product (Batch #6403)				Reference Product (Batch #Z31383LS)			
	Can 1	Can 2	Can 3	Mean	Can 1	Can 2	Can 3	Mean
Beg	3.42 [0.58]	3.17 [0.61]	3.23 [0.65]	3.27 (4.0) [0.61]	2.72 [1.26]	2.94 [1.10]	3.10 [0.77]	2.92 (6.5) [1.04]
Mid	3.08 [0.67]	3.29 [0.60]	3.25[3] [0.63]	3.21 (3.5) [0.63]	3.01 [0.81]	3.19 [1.00]	2.72 [1.01]	2.97 (8.0) [0.94]
End	3.27 [0.65]	3.08 [0.65]	3.27 0.65]	3.21 (3.4) [0.65]	2.82 [0.90]	2.96 [0.88]	2.93 [0.99]	2.90 (2.5) [0.92]
Mean	3.26	3.18	3.25	3.23	2.85	3.03	2.92	2.93

1 Span is given in brackets.
2 Particle size %CV is given in parentheses.

[3] Appears to be a mean result, not that of an individual experiment.

Comments:

1. The firm has reported 'best' runs, without stating the criteria for 'best.'
2. The firm should indicate whether the MDI canister is heated to
3. The median size volume distribution of the test product is about 0.3 microns larger than for the RLD. However, the mean span of the test product, 0.63, is smaller than that of the RLD, 0.97.

V. SINGLE STAGE IMPACTOR USP APPARATUS 2 IMPINGER): DEPOSITION OF EMITTED DOSE

The firm employed the Impinger (single stage impactor apparatus 2, USP Chapter <601> Aerosols/Physical Tests) to determine the deposition of the emitted dose. Drug deposited on stage 2 is less than 6.4 microns. Data are expressed as the amount of drug in stage 1 (upper chamber) and stage 2 (the lower chamber). The equations are presented on page 613, volume A8.2.

Table 10
Deposition of Emitted Dose*
(μg per actuation)

Deposition Stage	Test Product (Batch #6403)			Reference Product (Batch #Z31383LS)		
	Mean[•]	Range	%CV	Mean[•]	Range	%CV
Actuator	12.6	10.6-14.6	12.0	9.22	6.06-16.72	50.2
Upper Impinger (Stage 1)	40.9	38.4-44.3	5.75	33.2	29.0-37.8	9.79
Lower Impinger (Stage 2)	44.3	42.4-45.6	3.02	56.8	53.0-60.4	4.82
Unit Dose**	-	-	-	-	-	-
Respirable Percentage***	-	-	-	-	-	-

* Data are based on 5 canisters of test product and 5 canisters of RLD.

** USP <601> states that Unit Dose from mean data of Uniformity of Unit Spray Content study is to be used in calculation of Respirable Percentage.

*** USP <601> states that Respirable Percentage is to be calculated from the amount of drug in the lower impinger per discharge, as a percentage of the mean Unit Dose.

Comments:

1. The firm provides a mean Unit Dose of 90.44 µg for the test product and 97.29 µg for the RLD. The source for these numbers is not provided.

2. The firm reports Respirable Fraction data. However, in the absence of appropriate Unit Dose data, Respirable Fraction data cannot be calculated per USP recommendations.

3. Unit Dose data are requested for calculation of Respirable Fraction by the USP method. It is noted that comparative Unit Dose data for test and RLD products are provided in Volume B9.1, p. 21. However, the batch number of the RLD is not provided.

VI. SPRAY PATTERN AND PLUME GEOMETRY

A. Spray Pattern (12 Jun 95 submission)

The spray pattern and plume geometry are used to characterize the performance of the valve and actuator.

The spray pattern was determined on one spray per each of three canisters of test and RLD at each of three distances. Each can was placed in actuator and positioned, 2.5, 5.0 and 7.5 cm away and parallel to a 20 cm X 20 cm silica gel TLC spray. Single spray was fired (the canister was shaken before each spray) for each measurement. The resulting spots were viewed under UV light and the spray pattern was outlined with a pencil. Longest and shortest diameters of the spot were measured and the mean diameter was calculated.

Comment:

Freehand drawings of the spray patterns as submitted are imprecise and irregular, and cannot be interpreted. Data are unacceptable.

B. Spray Pattern (1 Aug 96 submission)

The firm was requested by letter of 18 Jul 96 to provide photographs of spray patterns. The firm conducted repeat spray patterns on the 'bio batches' of test and RLD products - these products were past their expiry dates at the time of retesting.

Comments:

1. Photographs of the data were submitted. Dimensions were based upon freehand drawings and do not appear from visual inspection to agree with the photographs. Accordingly, reported dimensions will not be tabulated.

2. Visual inspection of spray patterns reveals increasing diffuseness in the data for both test and RLD products as distance increases from 2.5 to 5.0 to 7.5 cm.

3. Comparative data are acceptable.

C. Plume Geometry

Per the 1989 *In Vitro* Guidance, firms were encouraged to submit data on plume geometry, although these data are optional. Plume geometry data were not submitted.

VII. POTENCY

Potency is defined as the average amount of drug delivered per spray. The results are expressed as percent of labeled amount of drug delivered from the mouthpiece per spray.

Three random cans were tested. The cans were weighed and shots were sampled at the beginning (10-11), middle (100-101) and end (199-200) sprays. The loss in each canister weight was recorded.

Table 11
Potency as measured by Amount of Drug Delivered
(weight loss data are also listed)

	Test Product (Batch #6403)				Reference Product (Batch #Z31383LS)			
	Shots #	Mean	Range	% CV	Mean	Range	% CV	Mean T/R
Drug Delivered (μg/spray)	Sprays 11-12 (3 cans)	82.8	81.1-84.4	2.0	91.2	89.6-91.9	1.4	0.91
	Sprays 100-101 (3 cans)	94.0	90.8-98.2	4.0	102.0	97.3-107.0	4.8	0.92
	Sprays 199-200 (3 cans)	107.4	106.0-108.8	1.3	98.7	96.6-99.7	1.6	1.09
Weight Loss (mg/spray)	Sprays 11-12 (3 cans)	87.0	85.8-88.7	1.8	85.0	83.9-85.8	1.2	1.02
	Sprays 100-101 (3 cans)	86.8	85.4-88.4	2.0	84.9	82.8-86.5	2.2	1.02
	Sprays 199-200 (3 cans)	86.1	84.0-88.0	2.3	84.4	83.3-85.7	1.4	1.02

Comments:

1. The firm used three cans to determine the drug potency. The 1989 guidance requests potency determination for ten test and ten reference canisters.
2. The method used for determination of potency failed Methods Validation. No further review will be conducted until Division of Chemistry determines that the method is validated.

VIII. *IN VITRO* DEFICIENCIES

1. Pivotal *in vitro* comparative cascade impactor data are unacceptable. The assay appears to be inadequately sensitive to quantitate drug on each stage of the cascade impactor. The firm's use of 25 actuations per study, in spite of the recommendation in the 1989 Division of Bioequivalence Guidance to use 15 actuations, emphasizes the need for improved assay sensitivity.

2. Material balance (USP 23 <601>), as requested in the 18 Jul 96 letter to the firm, was not provided. This calculation requires a knowledge of the actual shot weight, and measurement of drug concentration in the test and reference canisters. Drug concentration in the canisters is determined by assay of total drug in canister, and weight of total contents. The firm's reported "% mass balance (1 Aug 96 amendment, Comment # 1 section, pp. 2-3) is not consistent with the USP material balance calculation.

3. Specific observations and concerns with the cascade impactor data will be discussed with the firm in the meeting scheduled for 9 Sep 96.

4. Particle size distribution by laser diffraction reports "best 3 results" without providing criteria for selection of best runs. The result reported for canister # 3 (test product), middle canister sector, appears to be a mean result, not that of an individual experiment. No indication of specific station (actuation) numbers were provided to identify beginning, middle and end canister sectors.

5. USP 34 <601> requests for single stage impactor apparatus 2 that unit dose from mean data of the Uniformity of Unit Spray Content study be used in the calculation of Respirable Percentage. The firm states that the mean unit dose for test and RLD products is 90.44 μg for the test product and 97.29 μg for the RLD. It is noted that the firm did not conduct Uniformity of Unit Spray Content (USP <905>) on both test and RLD products, thus Respirable Percentage data cannot be determined based on the USP method. The source of the mean unit dose data is not apparent.

6. Potency/unit spray content data will not be reviewed until Division of Chemistry determines that the method is validated.

7. Specifications or revisions to specifications need to be considered for various tests, including respirable dose.

8. Particle size (distinct from particle size distribution) from the aerosol by

microscopy, a standard test recommended by USP <601> to reveal large solid particles and agglomerates, has not been provided.

IX. RECOMMENDATION

The firm should be informed of the *in vitro* deficiencies cited above.

Zakaria Z. Wahba, Ph.D.
Division of Bioequivalence
Review Branch III

Wallace P. Adams, Ph.D.
Office of Generic Drugs

RD INITIALED RMHATRE
FT INITIALED RMHATRF

9/3/96

Concur: _____ Date: 9/3/96
for Keith K. Chan, Ph.D.
Director
Division of Bioequivalence

cc: ANDA 73-045 (original, duplicate), HFD-600 (Hare), HFD-630, HFD-658 (Mhatre, Wahba), Drug File, Division File

ZZWahba/030796/032596/061096/070596/090396/file #73045sd3.695

SEP - 3 1996

Albuterol Inhalation Aerosol (MDI)
90 µg/actuation
ANDA 73-045
Reviewer: Z.Z. Wahba
73045s2.695

A.L. Laboratories
Baltimore, MD
Submission Dates:
June 12,1995
June 22,1995

Further Review for the In-Vivo Bioequivalence Study (Continuation of the Review Dated July 17, 1996)

I. BACKGROUND:

The firm submitted an application containing data from a pharmacodynamic bioequivalence study based on bronchoprovocation model employing a methacholine (MC) challenge methodology, and a safety evaluation study on its albuterol metered dose inhaler (MDI), 90 µg/actuation. The application also contains *in-vitro* performance data comparing the test product and the reference product, Ventolin® manufactured by Allen & Hanburys (a Division of Glaxo).

II. INTRODUCTION:

Albuterol is a synthetic sympathomimetic amine. It is a selective beta$_2$-adrenergic bronchodilator. It is administered either by inhalation or orally for the symptomatic relief of bronchospasm. When the drug is administered by inhalation, it produces significant bronchodilation in patients with reversible obstructive airway disease within 15 minutes and its effects are demonstrable for 3 to 4 hours. Its mechanism of action is due to its bronchodilation effect that results from relaxation of the smooth muscles of the bronchial tree. In patients with reversible airway obstruction, albuterol decreases resistance of the airways.

Each actuation delivers from the mouthpiece 90 µg of albuterol. Administration of albuterol MDI at recommended doses (one or two actuations) produces very low drug concentrations in accessible biological fluids such as blood or urine. Furthermore, following its topical application, the relevance of systemic levels of albuterol to its action in the lung is obscure. Therefore, on January 27, 1994, the Office of Generic Drugs issued a guidance to document the *in vivo* bioequivalence of multi-source albuterol MDI's based on pharmacodynamic methodology.

The 1994 OGD interim guidance recommended performance of two *in vivo* studies: (1) a pharmacodynamic bioequivalence study using a challenge (bronchoprovocation) design and (2) a safety evaluation study. This latter study is more appropriately termed a comparative systemic pharmacodynamic evaluation.

The two studies presented in this application are based on the 1994 OGD interim guidance.

III. OBJECTIVE:

The objective of the bronchoprovocation bioequivalence study is to demonstrate in vivo bioequivalence between the test product, A.L. Laboratories' Albuterol Metered Dose Inhaler (MDI) and the reference listed drug, Ventolin® Inhalation Aerosol.

IV. BRONCHOPROVOCATION BIOEQUIVALENCE STUDY:

A. Summary of Study Design:

Clinical study project #135-01-10647. The study protocol was reviewed and approved by the Institutional Review Board of the testing organization on May 02, 1994.

B. Protocol Title:

A bronchoprovocation study comparing two formulations of Albuterol Metered-Dose Aerosol Inhaler in patients with mild to moderate asthma.

C. Sponsor:

A.L. Laboratories, Inc.
The Johns Hopkins Bayview
Research Campus
333 Cassell Drive, Suite 3500
Baltimore, Maryland 21224

D. Clinical Facility:

E. Study Period:

May 1994 to May 1995

F. Subject Selection:

The subject selection criteria for this study were carried out according to the OGD guidance.

Patients were trained in the correct use of the MDI prior to

each day's testing with the InspirEase® training device to assure a consistent inspiratory flow rate and duration. For actual dosing, patients were required to place the inhaler in their mouths with their lips forming a seal around the mouthpiece. Patients were required to actuate the MDI and at the same time, start a slow sustained inhalation over a 6-9 second period. After inhalation, patients were required to hold their breath for 8-10 seconds before a controlled exhalation. The investigator and patients remained blinded as to which treatment was administered during each period.

BASELINE QUALIFICATION

Patients were required to perform repeated baseline FEV_1s at the start of each day. In most cases, three baseline FEV_1s were within 5% of each other.

Each study day consisted of a pre-albuterol methacholine challenge followed at least 3 hours later by administration of the assigned albuterol treatment and a post-albuterol methacholine challenge. Per protocol, each dosing period was separated by at least 24 hours. The reviewer notes, however, that the stated protocol would allow study day intervals of not less than 23 hours.

Before proceeding with the albuterol treatment on each day, subjects were required to meet the following baseline criteria:

1. An FEV_1[1] $\geq$ 80% of predicted value for age, height and gender.
2. An FEV_1 within 12% of the qualifying day FEV_1
3. FEV_1, due to the saline control not less than a 10% decrease from baseline FEV_1.
4. A pre-albuterol PD_{20}[2] within a four-fold dilution (25-400%) of the qualifying day PD_{20} (see Deviation from Subject Inclusion Criteria section J of this review).

FEV_1: Forced Expiratory Volume of the lung in one second.

PD_{20}: The cumulative dose of the challenge agent (methacholine) required to drop the FEV_1 value by 20% below the saline control FEV_1.

G. Study design:

Randomized, two-treatment, four-period, two-sequence, crossover double blind study on four separate days, employing 25 mild to moderate asthma patients. A single dose (90 µg/actuation) was administered during each treatment period.

Treatment Sequences:

Period	Visit 1	Visit 2	Visit 3	Visit 4
Sequence 1	T	R	R	T
Sequence 2	R	T	T	R

T=test product R=reference product

Dosing was performed for each patient at approximately the same time (within one hour) for each treatment period. On methacholine challenge days, dosing with albuterol MDI occurred 15 minutes prior to initiation of the methacholine challenge test.

Randomization:
a. Sequence #1: Subjects #102, 104, 105, 109, 114, 116, 118, 119, 121, 124, 126 and 127.

B. Sequence #2: Subjects #101, 103, 106, 108, 110, 113, 115, 117, 122, 123, 125, 128 and 129.

Canister Camouflage:
Canisters and actuators were camouflaged with silver colored, plastic coated cloth tape in such manner as not to interfere with product performance. It is also noted that test product and reference product actuators were both blue in color.

H. Treatment Plan: (vol. A8.1, page #030)

1. Bioeqivalence Study Products:

a. Test Product:

Albuterol Metered Dose Inhalation Aerosol.
90 µg/actuation
Manufacturer:
Lot #6403; Lot Size-total units filled units (Lot Size, minus rejects units); manufacture date: July 1993; Valve:
, Manufacturer:
Actuator:
Manufacturer:

Dose: one inhalation of A.L. Lab's albuterol MDI (90µg/actuation);

b. Reference Product:

Ventolin® (Albuterol Metered Dose Inhaler)
90 µg/actuation
Manufacturer: Allen & Hanburys, Division of Glaxo
Lot #Z31383LS
Expiration Date: March 1996

Dose: one inhalation of Ventolin® inhalation aerosol (90µg/actuation), Allen & Hanburys.

2. Other Drug Products:

a. Screening for the Dose Response:

Ventolin® Aerosol Inhaler
90 µg/actuation
Manufacturer: Allen & Hanburys, a Division of Glaxo
Lot #Z31443MS, Expiration Date: March 1996
Lot #Z31473MS, Expiration Date: March 1996
Lot #4ZPA183, Expiration Date: December 1996

b. Challenge Testing:

Product: Methacholine chloride (Provocholine®)
100 mg/5 mL vial for reconstitution
Manufacturer: Roche Laboratories
Lot #0033, Expiration Date: April 1, 1995
Lot #0038, Expiration Date: November 1, 1995

I. Subjects:

Demographic Information

The total number of patients screened for the study	**87** patients were screened but the firm's demographic table provided information for 84 patients only. Males= 34 Females= 50
Number of patients who failed screening and were discontinued	**58** subjects failed screening: Details a. **24** subjects had baseline FEV_1s less than 80% of predicted value b. **10** subjects failed to demonstrate a suitable airway response to doses of methacholine below 4 mg/ml c. **19** subjects failed to meet the necessary airway responsiveness to one or two actuations of albuterol d. **5** Subjects were ineligible because of medical issues (4 were over-weight and 1 was taking concomitant medication).
Number of Patients who passed the inclusion/ exclusion and screening criteria for entry the biostudy	**29** patients Males= **15** Females= **14**
Number of patients who completed the biostudy	**25** patients (#101-106, 108-110, 113-119, and 121-129)completed the biostudy. Males= **12** Females= **13** Out of 29 patients only 4 patients (#107,111, 112 and 120) did not complete the study for various reasons (for details see Vol. #8.1, p #076)

J. Deviation from Subject Inclusion Criteria:

1. Subject #103 did not meet the criteria of (PD_{20} after 2 actuations)/(baseline PD_{20}) $\geq$ 8.0 and (PD20 after 2 actuations)/(PD_{20} after 1 actuation) $\geq$ 2.0, the ratios were 7.4 and 1.8, respectively.

2. Subject #108 did not meet the criteria of (PD_{20} after 2 actuations)/(baseline PD_{20}) $\geq$ 8.0 and (PD20 after 2 actuations)/(PD_{20} after 1 actuation) $\geq$ 2.0, the ratios were 6.4 and 1.9, respectively.

3. Subject #119 did not meet the criteria of (PD_{20} after 2 actuations)/(baseline PD_{20}) $\geq$ 8.0, the ratio was 7.7.

4. There was a number of baseline PD_{20} on some study days that showed values outside the range of 50-200% of the qualifying day PD_{20} as recommended by the Interm Guidance. An amendment to the protocol was approved by the Institutional Review Board (IRB) for Human Subjects Research, on October 25, 1994 to broaden baseline PD_{20} criteria to be within a fourfold dilution (25-400%) of the value measured on the qualifying day. (See Vol. A8.1, Clinical Summary Section, page #072 and Clinical Appendix I, pages #147-149).

K. Visits Plan:

The twenty-five subjects who completed the biostudy did so in a minimum of 4 and a maximum of 7 visits. Eight, nine, five and three subjects completed the study in 4, 5, 6 and 7 visits, respectively.

L. Study Validation:

Validation of Methacholine (MC) challenge methodology was performed based on intra-day and inter-day reproductivity of MC PD_{20} values. FEV_1 measurements were used to evaluate the study validation.

Four subjects (#101, 102, 103 and 104) were used to evaluate the validation of the methacholine challenge method. Intra-day precision was evaluated by comparing two methacholine challenge tests conducted at an interval of at least three hours. Inter-day precision was measured by comparing the methacholine challenges tests conducted on five different days (Vol. A8.1, pp 114-146)). The arithmetic average of the PD_{20}s for intra-day CV was 64% and for inter-day was 68% (vol. A8.1, p 114).

ACCURACY OF DATA

PD_{20} values:

The pharmacodynamic data are given in this application in the form of MC PD_{20} values. The reviewer performed spot-check calculations to determine the accuracy of the PD_{20} values.

The sponsor calculated the PD_{20} values by linear interpolation between the last two FEV_1 values and the respective cumulative doses of methacholine.

To verify these data, the reviewer calculated the PD_{20} values using the following formula based on modification of a formula in HISTAMINE AND METHACHOLINE TESTS: Tidal Breathing Method, Laboratory Procedure and Standardisation, By E.F. Juniper, D.W. Cockcroft and F.E. Hargreave, 1991, p 28-29.

$$PD_{20} = D1 + \frac{(D2 - D1)(20 - R1)}{(R2 - R1)}$$

Where:

D1= second to last cumulative methacholine dose (<20% FEV_1 fall)
D2= last cumulative methacholine dose (>20% FEV_1 fall)
R1= % fall in FEV_1 after D1 relative to saline control.
R2= % fall in FEV_1 after D2 relative to saline control.

The results of calculations on random spot-check of validation study (pages 125-134, Vol. A8.1).

Data from FEV_1 Measurements for the Study Validation

Subject#	Treatment	Methacholine PD_{20} (mg)	
		Reviewer	Sponsor
1 (AM visit)	Ref.	0.0491	0.0439
1 (PM visit)	Ref.	0.0588	0.0589
2	Ref.	0.021	0.021
3	Test	0.0289	0.025
4	Ref.	0.0542	0.0540

Data from All Visits
(the following from PM visits only)

Subject#	Treatment	Methacholine PD_{20} (mg)	
		Reviewer	Sponsor
3	Test	0.2008	0.2010
5	Ref.	0.5831	0.3852
10	Test	0.0170	0.0152
18	Test	0.4409	0.3570
27	Ref.	1.2465	1.2430

Comment:

Based on the data provided, the reviewer cannot confirm some of the reported post-albuterol PD_{20} values. Note that, in the absence of the number of breaths associated with each methacholine dose, five breaths were assumed. (please see the Deficiency Section).

M. Statistical Analysis and Comparative In Vivo Performance:

As recommended by the 1994 OGD interim Guidance, the post-albuterol PD_{20} values of the in vivo performance of the test and reference listed products were used as the primary basis for bioequivalence evaluation. Data on the Drug Activity Ratios (DAR) have been analyzed and used as a secondary parameter for future reference.

The methacholine PD_{20} measured after the albuterol dose of the test product was compared to the same measurement after the reference product. The ratios of the post-albuterol PD_{20} to the pre-albuterol PD_{20}, Drug Activity ratio (DAR) for each treatment were also compared. The within product variances were also computed.

Individual subject PD_{20} values for the test and reference products are given in Table #1. The effect of length of time between two treatments of a given product on the stability of post-albuterol PD_{20} is given in Table #2 (the table shows the number of days between successive treatments of test and reference products). The relationship between length of dosing interval on the PD_{20} ratios of its first and second replicate treatments is given in Table #3.

Results of the relationship between length of dosing interval (in days) and the PD_{20} ratios of its first and second replicate treatments are displayed in Figure #1. This analysis was conducted to determine whether shorter intervals decreased variability in response.

The results of linear regression analysis indicated that there was no correlation between the length of dosing interval (in days) and the ratio of PD_{20} values for either product. Shorter intervals did not result in PD_{20} ratios closer to unity.

There are two ways to assess bioequivalence of MDI drugs based on pharmacodynamic measurements: (a) "response scale", and (b) "dose scale". In the "response scale" assessment, 90% confidence intervals are calculated for ratios of the test and reference products' values for a given pharmacodynamic metric, which is PD_{20} for the bronchoprovocation study under review. The "dose scale" assessment method involves extrapolation of the pharmacodynamic response to the dose axis, and calculation of the 90% confidence intervals for the bioavailability of the test product relative to that of the reference product. The agency has previously approved albuterol MDI studies based on either "response scale" or "dose scale".

In the present submission both the in vivo pharmacodynamic study and data analysis were conducted based on the 1994 OGD interim guidance. The statistical analysis that was used to determine bioequivalence of the test and reference products was based on the response scale approach.

It should be noted that "dose scale" assessment of bioequivalence is not necessary for this biostudy for the following reasons:

1. The firm has conducted the present study based on the 1994 OGD interim guidance which requires each subject to demonstrate dose response before inclusion of the subject in the study.

2. The biostudy has shown the ability of the subjects that were enrolled to distinguish between pharmacodynamic responses (PD_{20}) to one and two actuations of the reference product, the characteristic that is known as the "good detector".

3. Most of subjects have shown a minimum twofold ratio of response to two actuations relative to one actuation of Ventolin® Inhalation Aerosol.

4. The biostudy included spirometric controls for each study day to minimize the variability in drug response.

DATA AND STATISTICAL ANALYSIS:

The statistical analysis to determine bioequivalence of the test and reference products was based on the "response scale". Analyses of the data were performed by the Division of Biometrics, HFD-700.

The following statistical approaches were applied:
1. Conventional analyses employed for replicate design-based bioequivalence studies.
2. Scaling of the bioequivalence interval based on the intra-subject variability of the reference product.

The evaluation analyses are described below:

1. **Conventional analyses employed for replicate design-based bioequivalence studies:**

   The conventional analyses were performed with and without using the pre-albuterol PD_{20} as covariate. These analyses were carried out for log-transformed (Ln) post-albuterol PD_{20} and Drug Activity Ratio (DAR). In these analyses, two models were considered: (1) a model that assumed no period effect, and (2) a model that assumed that period effects might be present. Analyses were carried out using SAS PROC MIXED. The results of these analyses are summarized below in terms of point estimates and 90% confidence intervals for the ratio of test product average response over reference product average response.

a. Response Scale-Conventional Analyses without use of Pre-albuterol PD_{20} as Covariate

Model	Ln(Post-Albuterol PD_{20})		Ln (DAR)	
	Test/Ref	90% CI	Test/Ref	90% CI
No Period Effect	**80.90%**	**67.52, 96.92**	89.49%	73.12, 109.52
With period Effect	**81.14%**	**67.79, 97.12**	89.68%	72.99, 110.19

Comments:

i. Results of conventional analyses with or without period effect showed that the 90% confidence intervals for the log-transformed PD_{20} fall within the range of 67-150% previously considered by OGD for the approval of generic albuterol MDI's.

ii. Drug Activity Ratios (DAR) were calculated as secondary data analyses recommended in the OGD interim guidance. The DAR analysis is intended to assist an evaluation of adjustment of postdose PD_{20} for the baseline PD_{20} obtained on the same day. In addition, it serves as a potential future reference in the development of a bioequivalence standard for albuterol inhalation aerosols.

iii. Note: The 1994 OGD interim guidance states that the primary data analysis of given bioequivalence data should be based on postdose PD_{20}. These data are considered pivotal.

b. Response Scale-Conventional Analyses with use of Pre-albuterol PD_{20} as Covariate

Several analyses were carried out in which Ln(pre-albuterol PD_{20}) was used as a covariate. Point estimates and 90% confidence intervals using this approach were always the same for Ln-post albuterol PD_{20} and Ln-DAR . The specific values of the 90% confidence limits depended on which factors were included in the statistical model. For this study, the lower limit of the 90% confidence interval ranged from 70.48% to 72.16%, and the upper limit of the 90% confidence interval ranged from 101.61% to 106.56%, for the various models used. Thus, all of the confidence intervals obtained using Ln(pre-albuterol PD20) as a covariate fell within the limits

of 67% to 150%.

2. **Scaling Of Bioequivalence Limits to the Reference Product Within-Subject Standard Deviation:**

Two analyses were carried out for this scaling approach. The purpose of the two analyses is to assess whether bioequivalence had been demonstrated if the bioequivalence limits are scaled to the reference product within-subject standard deviation. These analyses used bootstrap methodology [specifically, the Bias-Corrected and Accelerated (BCa) method as described in the 1993 textbook of Efron and Tibshirani, 100,000 bootstrap samples per run] to obtain 90% confidence intervals for the quantity,

$$[\mathrm{Ln}(muT) - \mathrm{Ln}(muR)]/\sigma_{WR}$$

where: muT is the population geometric mean response for the Test product, muR is the population geometric mean response for the reference product, and σ_{WR} is the reference product within-subject standard deviation on the log scale. In the first analysis, it was assumed that there were no period effects in the study (Without Period Effect). In the second analysis, the analysis allowed for period effects (With Period Effect).

The 90% bootstrap confidence limits

Model	Metric	90% bootstrap confidence Limits (Ln-Units)
Without Period Effect	Post-albuterol PD_{20}	**-0.6935, -0.0658**
	DAR	-0.5287, 0.1385
With Period Effect	Post-albuterol PD_{20}	**-0.7625, -0.0504**
	DAR	-0.5673, 0.1790

The bioequivalence limits to which these confidence intervals are compared are plus-or-minus $(\ln 1.25)/\sigma_{W0}$.
For the choices of σ_{W0}= 0.30, 0.25 and 0.20 , these limits are as follows:

σ_{W0}	$(\text{Ln } 1.25)/\sigma_{W0}$	Bioequivalence Limits (Ln-units)
0.30	0.7438	-0.7438, 0.7438
0.25	0.8926	-0.8926, 0.8926
0.20	1.1157	-1.1157, 1.1157

Comments:

i. The scaling of bioequivalence limits become less stringent as the value of σ_{W0} is decreased, and more stringent as the value of σ_{W0} is increased.
Thus, a σ_{W0} =0.25 provides wider bioequivalence limits than does σ_{W0} =0.30.

ii. The confidence interval for the primary PD_{20} pharmacodynamic parameter analyzed without period effect falls within the limits corresponding to σ_{W0} = 0.30. When analyzed with a period effect, this parameter fails to fall within the limits corresponding to σ_{W0} = 0.30. It would pass the test for

σ_{WO}=0.293. Thus, both the products would pass the test for the less stringent limit of σ_{WO} = 0.25.

SUMMARY OF THE STATISTICAL ANALYSIS:

1. The bioequivalence evaluation for this study is based on "response scale".

2. For the pivotal post-dose PD_{20} data, the test product meets the OGD interim standard bioequivalence interval criteria of 67-150% set for albuterol metered dose inhalers. These criteria are based on data analyses with and without the assumption of period effects and with and without the use of pre-albuterol PD_{20} as covariate.

3. An alternative analysis, based on scaling the bioequivalence limits to the reference product's within-subject standard deviation, was conducted. The 90% confidence interval limits for the pivotal post-dose PD_{20} data assuming no period effects fell within the limits corresponding to σ_{WO} = 0.30. However, when period effects were assumed, the 90% confidence interval does not fall within the limit corresponding to σ_{WO} = 0.30. The product would however, pass the test for σ_{WO} = 0.293 or lower, a less stringent bioequivalence limit.

4. The above analyses are contingent upon validation of data requested in the Deficiency Section.

V. SAFETY EVALUATION STUDY:

The in vivo safety evaluation study conducted by A.L. Laboratories on its drug product, albuterol inhalation aerosol, 90 µg per actuation, lot #6403, comparing it to Ventolin® manufactured by Allen & Hanburys (a Division of Glaxo), has been found acceptable by the Division of Bioequivalence. (Based on the medical officer's review, in volume B9.1) .

VI. DEFICIENCIES:

The following items are needed for completion of the evaluation of the in vivo bioequivalence study. These items should be provided on paper copies (spread sheets) as well as on a floppy diskette (ASCII formate):

1. Complete raw data for all FEV_1 measurements, during screening and subject inclusion phases, and during the replicate design treatment phase for the 25 subjects used in the bioeqivalence

study. This should include baseline FEV_1 measurements for each study day including subject screening and inclusion phase, as well as all FEV_1 measurments associated with each and every challenge dose. The number of breaths of methacholine associated with each and every challenge dose should also be reported.

These data should include:

A. Raw data on subject inclusion qualification criteria showing that there was a minimum eight-fold increase over baseline in response to two actuations of Ventolin® Inhalation Aerosol and a minimum twofold ratio of response to two actuations relative to one actuation of Ventolin® Inhalation Aerosol. Include an example(s) of the method of calculation that was used for subject inclusion qualification criteria.

B. With regard to the data on the individual FEV_1 efforts for the bronchoprovocation study (Data submitted by the firm on June 19, 1995, in two tables, located in volume B9.1, p #05-#25).

i. For **Table #1** (baseline FEV_1 data prior to morning and afternoon challenges for treatment phases only).

The data for subjects #113, 114, 115, 116, 119, 121, 122 (visits 1, 2 and 3) and 123 are not provided.

ii. For **Table #2** (raw FEV_1 data for treatment phases only).

The data for subjects #113, 114, 115, 116, 119, 121, 122 (visits 1, 2 and 3) and 123 are not provided.

2. Please provide the equation that was used to estimate the Post-albuterol PD_{20} (cumulative mg). In addition, the firm should provide examples of its calculations for this value for a number of subjects. These examples should include subjects who had relatively high and relatively low post-albuterol PD_{20} values.

3. In the validation report section (Vol. A8.1, page #116), the firm is requested to provide equations and its calculations for subject #1, both morning and afternoon visits.

4. The raw data for the challenge studies should include the actual date of dosing of the treatment phase, gender and age, body weight, height, and predicted FEV_1 for age, gender and height, in addition to the data on baseline , saline control and FEV_1 at each challenge dose.

VII. RECOMMENDATION:

The in vivo bioequivalence study conducted by A.L. Laboratories on its drug product, albuterol inhalation aerosol, 90 µg per actuation, lot #6403, comparing it to Ventolin® manufactured by Allen & Hanburys (a Division of Glaxo), has been found incomplete by the Division of Bioequivalence for the deficiencies cited above.

The firm should be informed of the deficiencies and recommendation.

Zakaria Z. Wahba, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALED RMHATRE
FT INITIALED RMHATRE 9/3/96

Concur: _____ Date: 9/3/96
for Keith K. Chan, Ph.D.
Director
Division of Bioequivalence

cc: ANDA 73-045 (original, duplicate), HFD-600 (Hare), HFD-630, HFD-658 (Mhatre, Wahba), Drug File, Division File

ZZWahba/030796/032596/061096/070596/071596/082596/082996/
file #73045s2.695

ANDA: 73-045

Table #1

Albuterol Metered Dose Inhaler
Bronchoprovocation Study #135-01-10647
Daily Baseline Qualification Criteria During Bioequivalence Testing [A,B]

Subject	Pred FEV1	Qual Day Pre-A PD20	Qual Day FEV1	Product	Visit Date	Visit	Baseline FEV1	%(FEV1/ Pred FEV1) [1]	%Chg FEV1 /Qual Day FEV1 [2]	Saline FEV1	%Chg Saline FEV1 /Base FEV1 [3]	%(Pre-A PD20/ .Qual Day PD20) [4]	Pre-Albuterol PD20	Post-Albuterol PD20	Post-A PD20/ Pre-A PD20
101	3.93	0.0463	3.87	R	06MAY94	1	3.83	97	-1	3.83	0.0				
				R	10MAY94	1A	3.91	99	1	3.87	-1.0	167.0	0.0773	0.1840	2.4
				T	24MAY94	2	4.21	107	9	4.21	0.0	99.4	0.0460	0.0680	1.5
				T	02JUN94	3	3.90	99	1	3.81	-2.3	57.7	0.0267	0.1294	4.8
				R	08JUN94	4	3.79	96	-2	3.66	-3.4	89.2	0.0413	0.1270	3.1
102	4.32	0.0442	3.62	T	18MAY94	1	3.53	82	-2	3.36	-4.8	79.6	0.0352	0.3670	10.4
				R	15JUN94	2	3.49	81	-4	3.49	0.0	126.2	0.0558	0.1850	3.3
				R	21JUN94	3	3.62	84	0	3.66	1.1	58.1	0.0257	0.5930	23.1
				T	28JUN94	4	3.79	88	5	3.79	0.0	140.3	0.0620	0.2320	3.7
103	3.97	0.0160	4.21	R	20MAY94	1	4.17	105	-1	4.13	-1.0	455.0	0.0728		
				R	23MAY94	1A	3.74	94	-11	3.62	-3.2	91.3	0.0146	0.1790	12.3
				T	25MAY94	2	3.91	98	-7	3.83	-2.0	120.0	0.0192	0.2010	10.5
				T	07JUN94	3	3.83	96	-9	3.70	-3.4	80.6	0.0129		
				T	14JUN94	3A	4.09	103	-3	4.04	-1.2	63.1	0.0101	0.0652	6.5
				R	17JUN94	4	4.21	106	0	4.02	-4.5	269.4	0.0431		
				R	22JUN94	4A	4.26	107	1	4.13	-3.1	117.5	0.0188	0.1590	8.5
104	4.32	0.1820	3.87	T	23MAY94	1	3.83	89	-1	3.83	0.0	76.9	0.1400	6.8360	48.8
				R	25MAY94	2	3.70	86	-4	3.70	0.0	321.9	0.5858		
				R	31MAY94	2A	3.77	87	-3	3.90	3.4	56.9	0.1035	2.6840	25.9
				R	03JUN94	3	3.70	86	-4	3.70	0.0	89.6	0.1630	3.8360	23.5
				T	07JUN94	4	3.79	88	-2	3.87	2.1	168.8	0.3072	5.8000	18.9
105	3.31	0.0788	2.81	T	17JUN94	1	3.11	94	11	3.06	-1.6	223.4	0.1760		
				T	20JUN94	1A	2.81	85	0	2.89	2.8	106.7	0.0841	0.3138	3.7
				R	22JUN94	2	2.85	86	1	2.85	0.0	105.2	0.0829	0.3852	4.6
				R	29JUN94	3	2.77	84	-1	2.85	2.9	97.2	0.0766	0.7540	9.8

[A] Subjects were excluded from the study on a particular day if:
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[4] the pre-albuterol PD20 was outside 50 to 200%, but within 25 to 400%
(# - criteria prior to 25OCT94) or outside 25 to 400% (*) of the qualifying day PD20
[B] The abbreviations used on this listing are: Pred=Predicted, Pre-A=Pre-Albuterol, Post-A=Post-Albuterol, Base=Baseline
Qual Day=Screening Qualification Day Value (For a complete listing of all screening qualification data, refer to Appendix)

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Table # 1
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Albuterol Metered Dose Inhaler
Bronchoprovocation Study #135-01-10647
Daily Baseline Qualification Criteria During Bioequivalence Testing [A,B]

Subject	Pred FEV1	Qual Day Pre-A PD20	Qual Day FEV1	Product	Visit Date	Visit	Baseline FEV1	%(FEV1/ Pred FEV1) [1]	%Chg FEV1 /Qual Day FEV1 [2]	Saline FEV1	%Chg Saline FEV1 /Base FEV1 [3]	%(Pre-A PD20/ Qual Day PD20) [4]	Pre-Albuterol PD20	Post-Albuterol PD20	Post-A PD20/ Pre-A PD20
				T	06JUL94	4	2.72	82	-3	2.68	-1.5	105.7	0.0833	0.5530	6.6
106	2.56	0.0782	2.13	R	22JUN94	1	2.13	83	0	2.13	0.0	44.5	0.0348	0.4108	11.8
				T	07JUL94	2	2.17	85	2	2.13	-1.8	109.0	0.0852	0.8012	9.4
				T	12JUL94	3	2.00	78	-6	2.04	2.0	73.7	0.0576	1.3692	23.8
				R	14JUL94	4	2.17	85	2	2.04	-6.0	120.2	0.0940	1.4044	14.9
108	4.57	0.2310	3.73	R	10AUG94	1	3.66	80	-2	3.57	-2.5	162.8	0.3760	1.0390	2.8
				T	12AUG94	2	3.70	81	-1	3.66	-1.1	79.7	0.1840	1.1010	6.0
				T	15AUG94	3	3.62	79	-3	3.62	0.0	274.9	0.6350		
				T	16AUG94	3A	3.62	79	-3	3.53	-2.5	168.4	0.3890	1.6940	4.4
				R	22AUG94	4	3.60	79	-3	3.47	-3.6	168.4	0.3890	3.6180	9.3
109	4.57	0.0770	4.94	T	18AUG94	1	4.68	102	-5	4.81	2.8	248.1	0.1910		
				T	23AUG94	1A	4.85	106	-2	4.77	-1.6	94.8	0.0730	1.0390	14.2
				R	26AUG94	2	4.72	103	-4	4.68	-0.8	90.9	0.0700	0.4240	6.1
				R	31AUG94	3	4.77	104	-3	4.60	-3.6	213.0	0.1640		
				R	02SEP94	3A	4.85	106	-2	4.77	-1.6	129.5	0.0997	2.3940	24.0
				T	06SEP94	4	4.85	106	-2	4.77	-1.6	95.3	0.0734	1.5260	20.8
110	3.84	0.0066	3.57	R	19AUG94	1	3.53	92	-1	3.40	-3.7	215.2	0.0142		
				R	23AUG94	1A	2.68	70	-25						
				R	30AUG94	1B	3.23	84	-10	3.19	-1.2	145.5	0.0096	0.0317	3.3
				T	08SEP94	2	3.28	85	-8	3.23	-1.5	106.1	0.0070	0.0152	2.2
				T	15SEP94	3	3.66	95	3	3.53	-3.6	103.0	0.0068	0.0466	6.9
				R	20SEP94	4	3.66	95	3	3.49	-4.6	378.8	0.0250		
				R	27SEP94	4A	3.49	91	-2	3.23	-7.4	140.9	0.0093	0.0529	5.7
113	3.23	0.1770	2.79	R	15SEP94	1	2.40	74	-14						
				R	06OCT94	1A	2.64	82	-5	2.67	1.1	41.2	0.0730	0.5370	7.4

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[4] the pre-albuterol PD20 was outside 50 to 200%, but within 25 to 400% (# - criteria prior to 25OCT94) or outside 25 to 400% (*) of the qualifying day PD20
[B] The abbreviations used on this listing are: Pred=Predicted, Pre-A=Pre-Albuterol, Post-A=Post-Albuterol, Base=Baseline Qual Day=Screening Qualification Day Value (For a complete listing of all screening qualification data, refer to Appendix)

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Table # 1
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Albuterol Metered Dose Inhaler
Bronchoprovocation Study #135-01-10647
Daily Baseline Qualification Criteria During Bioequivalence Testing [A,B]

Subject	Pred FEV1	Qual Day Pre-A PD20	Qual Day FEV1	Product	Visit Date	Visit	Baseline FEV1	%(FEV1/ Pred FEV1)[1]	%Chg FEV1 /Qual Day FEV1[2]	Saline FEV1	%Chg Saline FEV1 /Base FEV1[3]	%(Pre-A PD20/ Qual Day PD20)[4]	Pre-Albuterol PD20	Post-Albuterol PD20	Post-A PD20/ Pre-A PD20
				T	13OCT94	2	2.76	85	-1	2.76	0.0	102.3	0.1810	1.4800	8.2
				T	10NOV94	3	2.57	80	-8	2.69	4.7	48.6	0.0860	0.6080	7.1
				R	17NOV94	4	2.71	84	-3	2.72	0.4	138.4	0.2450	0.5400	2.2
114	2.99	0.0070	3.29	T	22OCT94	1	3.54	118	8	3.47	-2.0	328.6	0.0230		
				T	24OCT94	1A	3.25	109	-1	3.08	-5.2	285.7	0.0200		
				T	29OCT94	1B	3.00	100	-9	2.87	-4.3	300.0	0.0210	0.0210	1.0
				R	12NOV94	2	3.09	103	-6	3.12	1.0	128.6	0.0090	0.0360	4.0
				R	29NOV94	3	3.20	107	-3	2.54	-20.6				
				R	03DEC94	3A	3.26	109	-1	3.29	0.9	228.6	0.0160	0.0330	2.1
				T	05DEC94	4	3.30	110	0	3.41	3.3	228.6	0.0160	0.0140	0.9
115	3.62	0.0280	3.04	R	08NOV94	1	2.56	71	-16						
				R	14NOV94	1A	3.14	87	3	3.02	-3.8	235.7	0.0660	0.3140	4.8
				T	07DEC94	2	3.04	84	0	2.94	-3.3	246.4	0.0690	0.1530	2.2
				T	04JAN95	3	2.77	77	-9	2.56	-7.6	114.3	0.0320	0.0860	2.7
				R	13JAN95	4	3.26	90	7	3.09	-5.2	67.9	0.0190	0.1070	5.6
116	2.49	0.0180	2.55	T	09NOV94	1	2.27	91	-11	2.20	-3.1	50.0	0.0090	0.0270	3.0
				R	11NOV94	2	2.24	90	-12	2.18	-2.7	44.4	0.0080	0.0580	7.3
				R	22NOV94	3	2.25	90	-12	2.31	2.7	94.4	0.0170	0.2610	15.4
				T	30NOV94	4	2.55	102	0	2.48	-2.7	155.6	0.0280	0.1520	5.4
117	3.94	0.3590	3.57	R	17NOV94	1	3.45	88	-3	3.49	1.2	301.9	1.0840	5.0400	4.6
				T	28NOV94	2	3.49	89	-2	3.32	-4.9	201.7	0.7240	1.0050	1.4
				T	30NOV94	3	3.45	88	-3	3.49	1.2	217.8	0.7820	0.8110	1.0
				R	02DEC94	4	3.53	90	-1	3.36	-4.8	790.0	2.8360		
				R	14DEC94	4A	3.49	89	-2	3.32	-4.9	228.4	0.8200	1.5200	1.9
118	2.75	0.0960	2.89	T	23NOV94	1	2.94	107	2	2.85	-3.1	53.1	0.0510	0.3570	7.0

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(# - criteria prior to 25OCT94) or outside 25 to 400% (*) of the qualifying day PD20
[B] The abbreviations used on this listing are: Pred-Predicted, Pre-A-Pre-Albuterol, Post-A-Post-Albuterol, Base-Baseline
Qual Day-Screening Qualification Day Value (For a complete listing of all screening qualification data, refer to Appendix)

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Table #1
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Albuterol Metered Dose Inhaler
Bronchoprovocation Study #135-01-10647
Daily Baseline Qualification Criteria During Bioequivalence Testing [A,B]

Subject	Pred FEV1	Qual Day Pre-A PD20	Qual Day FEV1	Product	Visit Date	Visit	Baseline FEV1	%(FEV1/ Pred FEV1)[1]	%Chg FEV1 /Qual Day FEV1[2]	Saline FEV1	%Chg Saline FEV1 /Base FEV1[3]	%(Pre-A PD20/ Qual Day PD20)[4]	Pre-Albuterol PD20	Post-Albuterol PD20	Post-A PD20/ Pre-A PD20
				R	28NOV94	2	2.64	96	-9	2.60	-1.5	18.0	0.0173		
				R	02DEC94	2A	2.85	104	-1	2.77	-2.8	190.6	0.1830	0.6770	3.7
				R	05DEC94	3	2.72	99	-6	2.72	0.0	176.0	0.1690	0.4250	2.5
				T	07DEC94	4	3.02	110	4	2.89	-4.3	136.5	0.1310	0.9490	7.2
119	4.48	0.0200	3.72	T	01DEC94	1	3.37	75	-9	3.37	0.0	70.0	0.0140	0.0180	1.3
				R	03DEC94	2	3.45	77	-7	3.42	-0.9	210.0	0.0420	0.0540	1.3
				R	29DEC94	3	3.22	72	-13						
				R	09JAN95	3A	3.12	70	-16						
				R	11JAN95	3B	3.52	79	-5	3.30	-6.3	105.0	0.0210	0.0770	3.7
				T	18JAN95	4	3.59	80	-3	3.53	-1.7	130.0	0.0260	0.0370	1.4
121	4.33	0.0500	3.74	T	20DEC94	1	3.71	86	-1	3.74	0.8	164.0	0.0820	0.2570	3.1
				R	22DEC94	2	3.70	85	-1	3.61	-2.4	272.0	0.1360	0.1030	0.8
				R	11JAN95	3	4.15	96	11	4.09	-1.4	368.0	0.1840	0.1750	1.0
				T	17JAN95	4	2.14	49	-43						
				T	23JAN95	4A	4.01	93	7	3.86	-3.7	170.0	0.0850		
				T	27JAN95	4B	3.74	86	0	3.80	1.6	166.0	0.0830	0.1620	2.0
122	3.97	0.1320	3.41	R	10JAN95	1	3.24	82	-5	3.30	1.9	136.4	0.1800	0.5650	3.1
				T	25JAN95	2	3.02	76	-11	2.92	-3.3	112.9	0.1490	0.1600	1.1
				T	01FEB95	3	3.03	76	-11	2.89	-4.6	57.6	0.0760	0.1440	1.9
				R	03FEB95	4	2.94	74	-14						
				R	13FEB95	4A	2.75	69	-19						
				R	21MAR95	4B	3.07	77	-10	2.92	-4.9	243.2	0.3210	0.4610	1.4
123	3.46	0.5020	3.17	R	18JAN95	1	2.90	84	-9	2.78	-4.1	67.3	0.3380	1.5360	4.5
				T	25JAN95	2	2.66	77	-16						
				T	27JAN95	2A	2.67	77	-16						

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Qual Day-Screening Qualification Day Value (For a complete listing of all screening qualification data, refer to Appendix)

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Albuterol Metered Dose Inhaler
Bronchoprovocation Study #135-01-10647
Daily Baseline Qualification Criteria During Bioequivalence Testing [A,B]

Subject	Pred FEV1	Qual Day Pre-A PD20	Qual Day FEV1	Product	Visit Date	Visit	Baseline FEV1	%(FEV1/ Pred FEV1) [1]	%Chg FEV1 /Qual Day FEV1 [2]	Saline FEV1	%Chg Saline FEV1 /Base FEV1 [3]	%(Pre-A PD20/ Qual Day PD20) [4]	Pre-Albuterol PD20	Post-Albuterol PD20	Post-A PD20/ Pre-A PD20
				T	31JAN95	2B	2.81	81	-11	2.73	-2.8	46.4	0.2330	3.3020	14.2
				T	02FEB95	3	2.83	82	-11	2.73	-3.5	59.8	0.3000	1.1390	3.8
				R	07FEB95	4	2.92	84	-8	2.90	-0.7	25.1	0.1260	0.9050	7.2
124	2.69	0.2860	3.49	T	07MAR95	1	3.29	122	-6	3.26	-0.9	99.0	0.2830	1.6920	6.0
				R	14MAR95	2	3.44	128	-1	3.41	-0.9	187.4	0.5360	0.5360	1.0
				R	21MAR95	3	3.21	119	-8	3.07	-4.4	113.6	0.3250	2.2610	7.0
				T	27MAR95	4	3.23	120	-7	3.18	-1.5	95.1	0.2720	1.5600	5.7
125	3.33	0.0480	2.77	R	14MAR95	1	2.65	80	-4	2.82	6.4	87.5	0.0420	0.0990	2.4
				T	20MAR95	2	2.72	82	-2	2.66	-2.2	87.5	0.0420	0.1950	4.6
				T	27MAR95	3	2.71	81	-2	2.70	-0.4	58.3	0.0280	0.1610	5.8
				R	04APR95	4	2.59	78	-6	2.69	3.9	72.9	0.0350	0.1860	5.3
126	4.27	0.0480	3.72	T	31MAR95	1	3.76	88	1	3.59	-4.5	166.7	0.0800	0.3520	4.4
				R	05APR95	2	3.58	84	-4	3.53	-1.4	120.8	0.0580	0.5610	9.7
				R	07APR95	3	3.71	87	0	3.78	1.9	120.8	0.0580	0.3900	6.7
				T	12APR95	4	3.97	93	7	4.06	2.3	116.7	0.0560	0.5000	8.9
127	3.38	0.2160	3.39	T	01APR95	1	3.35	99	-1	3.27	-2.4	77.8	0.1680	1.3360	8.0
				R	08APR95	2	3.33	99	-2	3.37	1.2	87.0	0.1880	1.2430	6.6
				R	11APR95	3	3.21	95	-5	3.15	-1.9	98.6	0.2130	2.2840	10.7
				T	22APR95	4	3.13	93	-8	3.26	4.2	85.2	0.1840	0.6050	3.3
128	3.71	0.0160	2.95	R	01APR95	1	2.81	76	-5	2.91	3.6	143.8	0.0230	0.1660	7.2
				T	08APR95	2	2.85	77	-3	2.80	-1.8	181.3	0.0290	0.0890	3.1
				T	13APR95	3	2.83	76	-4	2.80	-1.1	168.8	0.0270	0.0860	3.2
				R	22APR95	4	2.69	73	-9	2.62	-2.6	500.0	0.0800		
				R	29APR95	4A	2.67	72	-9	2.64	-1.1	93.8	0.0150	0.1250	8.3
129	3.18	0.2220	3.47	R	03APR95	1	3.27	103	-6	3.32	1.5	132.9	0.2950	1.2470	4.2

[A] Subjects were excluded from the study on a particular day if:
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[3] there was a greater then 10% drop in FEV1 post-saline administration
[4] the pre-albuterol PD20 was outside 50 to 200%, but within 25 to 400%
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Bronchoprovocation Study #135-01-10647
Daily Baseline Qualification Criteria During Bioequivalence Testing [A,B]

Subject	Pred FEV1	Qual Day Pre-A PD20	Qual Day FEV1	Product	Visit Date	Visit	Baseline FEV1	%(FEV1/ Pred FEV1)[1]	%Chg FEV1 /Qual Day FEV1[2]	Saline FEV1	%Chg Saline FEV1 /Base FEV1[3]	%(Pre-A PD20/ .Qual Day PD20)[4]	Pre-Albuterol PD20	Post-Albuterol PD20	Post-A PD20/ Pre-A PD20
				T	05APR95	2	3.47	109	0	3.36	-3.2	105.9	0.2350	0.5380	2.3
				T	11APR95	3	3.24	102	-7	3.22	-0.6	144.1	0.3200	1.2530	3.9
				R	13APR95	4	3.34	105	-4	3.35	0.3	169.4	0.3760	1.1850	3.2

[A] Subjects were excluded from the study on a particular day if:
[1] the baseline FEV1 was < 70% of predicted
[2] there was a greater than 12% change in FEV1 from the qualifying day FEV1
[3] there was a greater then 10% drop in FEV1 post-saline administration
[4] the pre-albuterol PD20 was outside 50 to 200%, but within 25 to 400%
(@ - criteria prior to 25OCT94) or outside 25 to 400% (*) of the qualifying day PD20
[B] The abbreviations used on this listing are: Pred=Predicted, Pre-A=Pre-Albuterol, Post-A=Post-Albuterol, Base=Baseline
Qual Day=Screening Qualification Day Value (For a complete listing of all screening qualification data, refer to Appendix)

ANDA # 73-045

Table # 2

number of days between treatments ↓

/*Broncho	Study	#135-01-1	Bioequivalence	Phase	Visit	Meeting	Qualificati	Criteria	*/	
/*subject	seq	product	vdate	visit	svisit	pd20	apd20	fev1	sfev1*/	
101	2	2	18-May-94	1A	1	0.0773	0.184	3.91	3.87	0
101	2	1	24-May-94	2	2	0.046	0.068	4.21	4.21	-6
101	2	1	2-Jun-94	3	3	0.0267	0.1294	3.9	3.81	-15
101	2	2	8-Jun-94	4	4	0.0413	0.127	3.79	3.66	-21
102	1	1	18-May-94	1	1	0.0352	0.367	3.53	3.36	0
102	1	2	15-Jun-94	2	2	0.0558	0.185	3.49	3.49	-28
102	1	2	21-Jun-94	3	3	0.0257	0.593	3.62	3.66	-34
102	1	1	28-Jun-94	4	4	0.062	0.232	3.79	3.79	-41
103	2	2	23-May-94	1A	1	0.0146	0.179	3.74	3.62	0
103	2	1	25-May-94	2	2	0.0192	0.201	3.91	3.83	-2
103	2	1	14-Jun-94	3A	3	0.0101	0.0652	4.09	4.04	-22
103	2	2	22-Jun-94	4A	4	0.0188	0.159	4.26	4.13	-30
104	1	1	23-May-94	1	1	0.14	6.836	3.83	3.83	0
104	1	2	31-May-94	2A	2	0.1035	2.684	3.77	3.9	-8
104	1	2	3-Jun-94	3	3	0.163	3.836	3.7	3.7	-11
104	1	1	7-Jun-94	4	4	0.3072	5.8	3.79	3.87	-15
105	1	1	20-Jun-94	1A	1	0.0841	0.3138	2.81	2.89	0
105	1	2	22-Jun-94	2	2	0.0829	0.3852	2.85	2.85	-2
105	1	2	29-Jun-94	3	3	0.0766	0.754	2.77	2.85	-9
105	1	1	6-Jul-94	4	4	0.0833	0.553	2.72	2.68	-16
106	2	2	22-Jun-94	1	1	0.0348	0.4108	2.13	2.13	0
106	2	1	7-Jul-94	2	2	0.0852	0.8012	2.17	2.13	-15
106	2	1	12-Jul-94	3	3	0.0576	1.3892	2	2.04	-20
106	2	2	14-Jul-94	4	4	0.094	1.4044	2.17	2.04	-22
108	2	2	10-Aug-94	1	1	0.376	1.039	3.66	3.57	0
108	2	1	12-Aug-94	2	2	0.184	1.101	3.7	3.66	-2
108	2	1	16-Aug-94	3A	3	0.389	1.694	3.62	3.53	-6
108	2	2	22-Aug-94	4	4	0.389	3.618	3.6	3.47	-12
109	1	1	23-Aug-94	1A	1	0.073	1.039	4.85	4.77	0
109	1	2	26-Aug-94	2	2	0.07	0.424	4.72	4.68	-3
109	1	2	2-Sep-94	3A	3	0.0997	2.394	4.85	4.77	-10
109	1	1	6-Sep-94	4	4	0.0734	1.526	4.85	4.77	-14
110	2	2	30-Aug-94	1B	1	0.0096	0.0317	3.23	3.19	0
110	2	1	8-Sep-94	2	2	0.007	0.0152	3.28	3.23	-9
110	2	1	15-Sep-94	3	3	0.0068	0.0466	3.66	3.53	-16
110	2	2	27-Sep-94	4A	4	0.0093	0.0529	3.49	3.23	-28
113	2	2	6-Oct-94	1A	1	0.073	0.537	2.64	2.67	0
113	2	1	13-Oct-94	2	2	0.181	1.48	2.76	2.76	-7
113	2	1	10-Nov-94	3	3	0.086	0.608	2.57	2.69	-35
113	2	2	17-Nov-94	4	4	0.245	0.54	2.71	2.72	-42
114	1	1	29-Oct-94	1B	1	0.021	0.021	3	2.87	0
114	1	2	12-Nov-94	2	2	0.009	0.036	3.09	3.12	-14
114	1	2	3-Dec-94	3A	3	0.016	0.033	3.26	3.29	-35
114	1	1	5-Dec-94	4	4	0.016	0.014	3.3	3.41	-37
115	2	2	14-Nov-94	1A	1	0.066	0.314	3.14	3.02	0
115	2	1	7-Dec-94	2	2	0.069	0.153	3.04	2.94	-23
115	2	1	4-Jan-95	3	3	0.032	0.086	2.77	2.58	-51
115	2	2	13-Jan-95	4	4	0.019	0.107	3.26	3.09	-60
116	1	1	9-Nov-94	1	1	0.009	0.027	2.27	2.2	0

ANDA #73-045

Table # 2
(Continue)

number of days between treatments ↓

116	1	2	11-Nov-94	2	2	0.008	0.058	2.24	2.18	-2	
116	1	2	22-Nov-94	3	3	0.017	0.261	2.25	2.31	-13	
116	1	1	30-Nov-94	4	4	0.028	0.152	2.55	2.48	-21	
117	2	2	17-Nov-94	1	1	1.084	5.04	3.45	3.49	0	7
117	2	1	28-Nov-94	2	2	0.724	1.005	3.49	3.32	-11	
117	2	1	30-Nov-94	3	3	0.782	0.811	3.45	3.49	-13	
117	2	2	14-Dec-94	4A	4	0.82	1.52	3.49	3.32	-27	
118	1	1	23-Nov-94	1	1	0.051	0.357	2.94	2.85	0	3
118	1	2	2-Dec-94	2A	2	0.183	0.677	2.85	2.77	-9	
118	1	2	5-Dec-94	3	3	0.169	0.425	2.72	2.72	-12	
118	1	1	7-Dec-94	4	4	0.131	0.949	3.02	2.89	-14	
119	1	1	1-Dec-94	1	1	0.014	0.018	3.37	3.37	0	9
119	1	2	3-Dec-94	2	2	0.042	0.054	3.45	3.42	-2	
119	1	2	11-Jan-95	3B	3	0.021	0.077	3.52	3.3	-41	
119	1	1	18-Jan-95	4	4	0.026	0.037	3.59	3.53	-48	
121	1	1	20-Dec-94	1	1	0.082	0.257	3.71	3.74	0	1
121	1	2	22-Dec-94	2	2	0.136	0.103	3.7	3.81	-2	
121	1	2	11-Jan-95	3	3	0.184	0.175	4.15	4.09	-22	
121	1	1	27-Jan-95	4B	4	0.083	0.162	3.74	3.8	-38	
122	2	2	10-Jan-95	1	1	0.18	0.565	3.24	3.3	0	2
122	2	1	25-Jan-95	2	2	0.149	0.16	3.02	2.92	-15	
122	2	1	1-Feb-95	3	3	0.076	0.144	3.03	2.89	-22	
122	2	2	21-Mar-95	4B	4	0.321	0.461	3.07	2.92	-70	
123	2	2	18-Jan-95	1	1	0.338	1.536	2.9	2.78	0	3
123	2	1	31-Jan-95	2B	2	0.233	3.302	2.81	2.73	-13	
123	2	1	2-Feb-95	3	3	0.3	1.139	2.83	2.73	-15	
123	2	2	7-Feb-95	4	4	0.126	0.905	2.92	2.9	-20	
124	1	1	7-Mar-95	1	1	0.283	1.692	3.29	3.26	0	4
124	1	2	14-Mar-95	2	2	0.536	0.536	3.44	3.41	-7	
124	1	2	21-Mar-95	3	3	0.325	2.281	3.21	3.07	-14	
124	1	1	27-Mar-95	4	4	0.272	1.58	3.23	3.18	-20	
125	2	2	14-Mar-95	1	1	0.042	0.099	2.85	2.82	0	5
125	2	1	20-Mar-95	2	2	0.042	0.195	2.72	2.66	-6	
125	2	1	27-Mar-95	3	3	0.028	0.161	2.71	2.7	-13	
125	2	2	4-Apr-95	4	4	0.035	0.186	2.59	2.69	-21	
126	1	1	31-Mar-95	1	1	0.08	0.352	3.76	3.59	0	6
126	1	2	5-Apr-95	2	2	0.058	0.561	3.58	3.53	-5	
126	1	2	7-Apr-95	3	3	0.058	0.39	3.71	3.78	-7	
126	1	1	12-Apr-95	4	4	0.056	0.5	3.97	4.06	-12	
127	1	1	1-Apr-95	1	1	0.168	1.336	3.35	3.27	0	7
127	1	2	8-Apr-95	2	2	0.188	1.243	3.33	3.37	-7	
127	1	2	11-Apr-95	3	3	0.213	2.284	3.21	3.15	-10	
127	1	1	22-Apr-95	4	4	0.184	0.605	3.13	3.26	-21	
128	2	2	1-Apr-95	1	1	0.023	0.166	2.81	2.91	0	8
128	2	1	8-Apr-95	2	2	0.029	0.089	2.85	2.8	-7	
128	2	1	13-Apr-95	3	3	0.027	0.086	2.83	2.8	-12	
128	2	2	29-Apr-95	4A	4	0.015	0.125	2.87	2.64	-28	
129	2	2	3-Apr-95	1	1	0.295	1.247	3.27	3.32	0	9
129	2	1	5-Apr-95	2	2	0.235	0.538	3.47	3.36	-2	
129	2	1	11-Apr-95	3	3	0.32	1.253	3.24	3.22	-8	
129	2	2	13-Apr-95	4	4	0.376	1.185	3.34	3.35	-10	

Table # 3

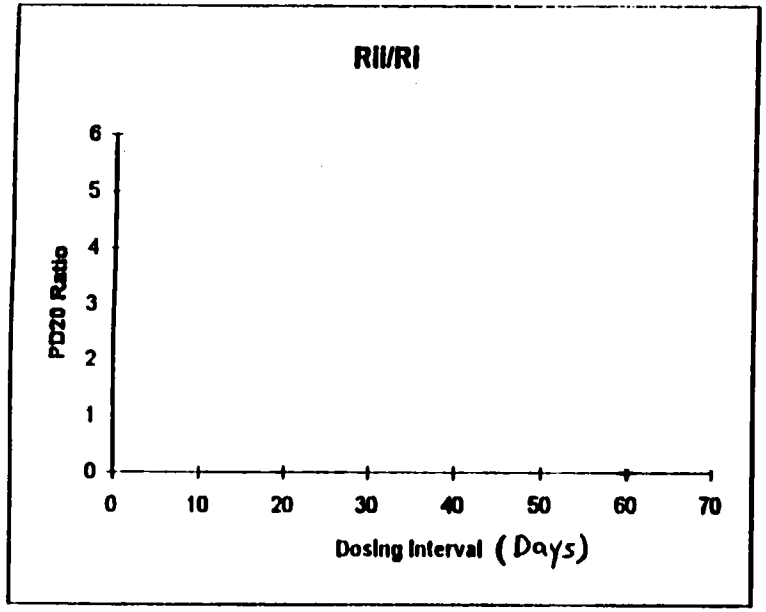
Ratios of PD20 & DAR values for the test and reference productsat at one actuation and time intervals between the replicate doses (ANDA #73045)

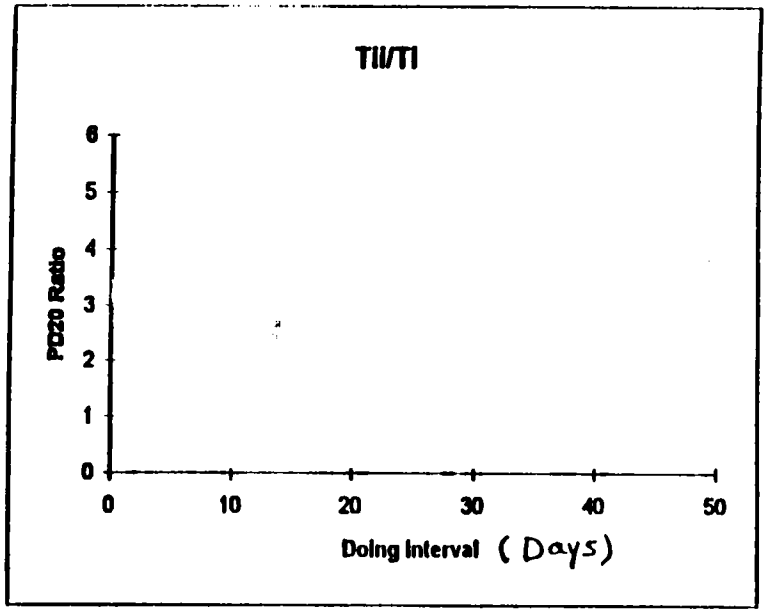
SUB	Time Interval (days) (Tii-Ti)	Tii/Ti		Time Interval (days) (Rii-Ri)	Rii/Ri	
		PD20	DAR		PD20	DAR
101	9	1.90	3.28	21	0.89	1.29
102	41	0.83	0.36	6	3.21	6.96
103	20	0.32	0.82	30	0.89	0.89
104	15	0.85	0.39	3	1.43	0.91
105	16	1.76	1.78	7	1.96	2.12
106	5	1.71	2.53	22	3.42	1.27
108	4	1.54	0.73	12	3.48	3.37
109	14	1.47	1.46	7	5.65	3.96
110	7	3.07	3.16	28	1.67	1.72
113	28	0.41	0.86	42	1.01	0.30
114	37	0.67	0.88	21	0.92	0.52
115	28	0.56	1.21	60	0.34	1.18
116	21	5.63	1.81	11	4.50	2.12
117	2	0.81	0.75	27	0.30	0.40
118	14	2.66	1.03	3	0.83	0.88
119	48	2.06	1.11	39	1.43	2.85
121	38	0.83	0.82	20	1.70	1.26
122	7	0.90	1.76	70	0.82	0.46
123	2	0.34	0.27	20	0.59	1.58
124	20	0.92	0.96	7	4.22	6.96
125	7	0.83	1.24	21	1.88	2.25
126	12	1.42	2.03	2	0.70	0.70
127	21	0.45	0.41	3	1.84	1.62
128	5	0.97	1.04	28	0.75	1.15
129	6	2.33	1.71	10	0.95	0.75
Mean	17.08	1.39	1.28	20.8	1.8	1.88
STD	13.09	1.16	0.82	17.50	1.45	1.79
%CV	77	83	64	84	81	95
Min	2	0.32	0.27	2	0.3	0.3
Max	48	5.63	3.28	70	5.65	6.96

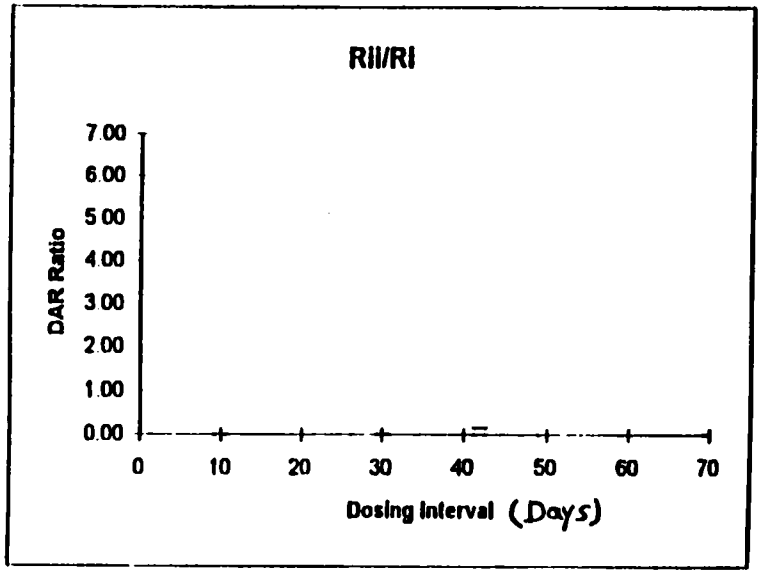
Ti Test product response, first dose
Tii Test product response, second dose
Ri Reference product response, first dose
Rii Reference product response, second dose

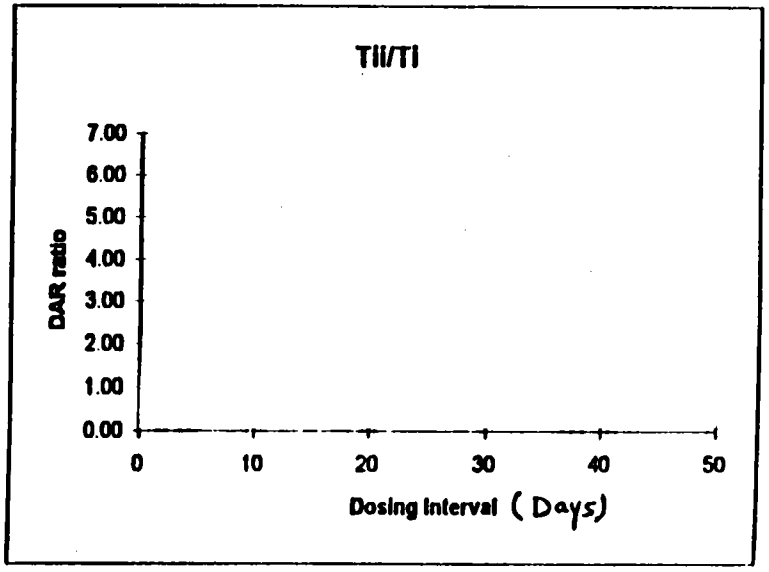
Figure #1

Ratios of PD20 & DAR values for the test and reference productsat at one actuation and time intervals between the replicate doses (ANDA #73045)









Ti Test product response, first dose
Tii Test product response, second dose
Ri Reference product response, first dose
Rii Reference product response, second dose

9N

JUL 17 1996

Albuterol Inhalation Aerosol
90 µg/actuation
ANDA 73-045
Reviewer: Z.Z. Wahba
73045s.695

A.L. Laboratories
Submission Dates:
June 12, 1995
June 22,1995

Review of a Pharmacodynamic Study and In Vitro Study Data for Bioequivalence Determination

I. OBJECTIVE:

To review the comparative in vivo and in vitro performance studies A.L. Laboratories' Albuterol Metered Dose Inhaler (MDI) relative to that of the reference listed drug, Ventolin® Inhalation Aerosol Inhaler.

II. IN VIVO COMPARATIVE STUDY:

SUMMARY OF STUDY DESIGN:
Clinical study project #135-01-10647

A. Protocol Title:

A bronchoprovocation study comparing two formulations of Albuterol Metered-Dose Aerosol Inhaler in patients with mild to moderate asthma.

B. Sponsor:

A.L. Laboratories, Inc.
The Johns Hopkins Bayview
Research Campus
333 Cassell Drive, Suite 3500
Baltimore, Maryland 21224

C. Clinical Facility:

D. Study Period:

May 1994 to May 1995

E. Study design:

Randomized, two-treatment, four-period, two-sequence, crossover double blind study on four separate days, employing 25 mild to moderate asthma patients. A single

dose (90 µg/actuation) was administered during each treatment period.

Treatment Sequences:

Period	Visit 1	Visit 2	Visit 3	Visit 4
Sequence 1	T	R	R	T
Sequence 2	R	T	T	R

T=test product R=reference product

F. Treatment Plan:

a. **Bioeqivalence Study Products:**

i. **Test Product:**

Albuterol Metered Dose Inhaler
90 µg/actuation
Manufacturer:
for A.L. Laboratories, Inc.
Lot #6403

ii. **Reference Product:**

Ventolin® (Albuterol Metered Dose Inhaler)
90 µg/actuation
Manufacturer: Allen & Hanburys, Division of Glaxo
Lot #Z31383LS
Expiration Date: March 1996

b. **Other Drug Products:**

i. **Screening for the Dose Response:**

Ventolin® Aerosol Inhaler
90 µg/actuation
Manufacturer: Allen & Hanburys, a Division of Glaxo
Lot #Z31443MS, Expiration Date: March 1996
Lot #Z31473MS, Expiration Date: March 1996
Lot #4ZPA183, Expiration Date: December 1996

ii. **Challenge Testing:**

Product: Methacholine chloride (Provocholine®)
100 mg/5 mL vial for reconstitution
Manufacturer: Roche Laboratories
Lot #0033, Expiration Date: April 1, 1995
Lot #0038, Expiration Date: November 1, 1995

G. Brief Summary of the Study Conduct:

Drug Administration

Patients were trained in the correct use of the MDI prior to each day's testing. For actual dosing, patients were required to place the inhaler in their mouths with their lips forming a seal around the mouthpiece. Patients were

required to activate the MDI at the same time, starting a slow sustained inhalation over a 6-9 second period. After inhalation patients were required to hold their breath for 8-10 seconds before a controlled exhalation. The investigator and patients remained blinded as to which treatment was administered during each period.

Dosing was performed for each patient at approximately the same time for each treatment period. On methacholine challenge days, dosing with albuterol MDI occurred 15 minutes prior to initiation of the methacholine challenge test.

Baseline Qualification
Patients were required to perform repeated baseline FEV_1s at the start of each day. In most cases, three baseline FEV_1s were within 5% of each other.

Each study day consisted of a pre-albuterol methacholine challenge followed at least 3 hours later by administration of the assigned albuterol treatment and a post-albuterol methacholine challenge. Each dosing period was separated by at least 24 hours.

Before proceeding with the albuterol treatment on each day, subjects were required to meet the following baseline criteria:
a. An FEV1 $\geq$ 80% of predicted value for age, height and gender.
b. An FEV1 within 12% of the qualifying FEV1
c. FEV_1 due to the saline control not less than a 10% decrease from baseline FEV_1.
d. A pre-albuterol PD20 within a four-fold dilution (25-400%) of the qualifying PD20 (see Deviation from Subject Inclusion Criteria section).

The methacholine PD20 measured after the albuterol dose of the test product was compared to the same measurement after the reference product. The ratios of the post-albuterol PD20 to the pre-albuterol PD20 for each treatment were also compared. The within product variances were also computed.

H. Subjects:

A total of 87 patient volunteers were screened for the study. Twenty-nine met the inclusion/exclusion criteria. Of the 58 patients who failed screening, 24 had baseline FEV_1s less than 80% of predicted value, 10 failed to demonstrate a suitable airway response to doses of methacholine below 4 mg/mL, 19 failed to meet the necessary airway responsiveness to one and two actuations of albuterol

and 5 patients were ineligible because of medical issues (4 were over-weight, 1 was taking concomitant medication).

Twenty-nine subjects met the dose-response criteria for entry into the bioequivalence study. However, only twenty-five subjects completed the bioequivalence study. Four subjects (#107, #111, #112 and #120) did not complete the bioequivalence study for various reasons (for details see Vol. #8.1, p #076).

Demographic Information

The total number of patients screened for the study	The firm mentioned that 87 patients were screened but the firm's demographic table provided information for 84 patients only. Males= 34 Females= 50
Number of patients who failed screening and were discontinued	**58** subjects failed screening: Details a. **24** subjects had baseline FEV$_1$s less than 80% of predicted value b. **10** subjects failed to demonstrate a suitable airway response to doses of methacholine below 4 mg/mL c. **19** subjects failed to meet the necessary airway responsiveness to one or two actuations of albuterol d. **5** Subjects were ineligible because of medical issues (4 were over-weight and 1 was taking concomitant medication).
Number of Patients who passed the inclusion/ exclusion and screening criteria for entry the biostudy	**29** patients Males= **15** Females= **14**
Number of patients who completed the biostudy	**25** patients (#101-106, 108-110, 113-119, and 121-129)completed the biostudy. Males= **12** Females= **13** Out of 29 patients only 4 patients (#107,111, 112 and 120) did not complete the study for various reasons (for details see Vol. #8.1, p #076)

I. **Deviation from Subject Inclusion Criteria:**

1. Subject #103 did not meet the criteria of (PD_{20} after 2 actuations)/(baseline PD_{20}) $\geq$ 8.0 and (PD_{20} after 2 actuations)/(PD_{20} after 1 actuation) $\geq$ 2.0, the ratio were 7.4 and 1.8, respectively.

2. Subject #108 did not meet the criteria of (PD_{20} after 2 actuations)/(baseline PD_{20}) $\geq$ 8.0 and (PD_{20} after 2 actuations)/(PD_{20} after 1 actuation) $\geq$ 2.0, the ratio were 6.4 and 1.9, respectively.

3. Subject #119 did not meet the criteria of (PD_{20} after 2 actuations)/(baseline PD_{20}) $\geq$ 8.0, the ratio was 7.7.

4. There was a number of baseline PD_{20} on some study days that showed values outside the range of 50-200% of the qualifying day PD_{20}.

J. **Visits Plan:**

The twenty-five subjects who completed the biostudy did so in a minimum of 4 and a maximum of 7 visits. Eight, nine, five and three subjects completed the study in 4, 5, 6 and 7 visits, respectively.

K. **Adverse Events:** (page #087, vol. 8.1)

See Attachment #1

L. **Study Validation:**

Four subjects (#101, 102, 103 and 105) were used to evaluate the intra- and interday precision of the methacholine challenge method. Intraday precision was evaluated by comparing two baseline methacholine challenges conducted at an interval of at least three hours. Interday precision was measured by comparing the baseline evaluation of the patient on five different days (see Attachment #2).

M. DATA ANALYSIS:

The statistical analysis for 25 subjects are presented in the following table.

Statistical Analysis Results (n=25)

Measurements (Logarithms)	Test Mean (Antiln)	Ref. Mean (Antiln)	T/R	Signif. (alpha=0.05)	Power%	90% C.I.
Pre-albuterol PD_{20}	-2.65715 (**0.070***)	-2.55713 (**0.078***)	0.90	NS	71	**0.79-1.03**
Post-albuterol PD_{20}	-1.15123 (**0.316***)	-0.94227 (**0.390***)	0.81	NS	<50	**0.68-0.98**
Post-/Pre-albuterol PD_{20}	1.50592 (**4.508***)	1.61487 (**5.027***)	0.90	NS	<50	**0.73-1.10**

Based on least squares means of logarithmically transformed data.
* mg of methacholine required to invoke the PD_{20} response.

General Comments on the Statistical Analysis Data of the 25 Subjects:

1. For Intra-subject, Within-Product Variability (n=25):
The within subject variances in post-albuterol PD_{20} were 0.26698 and 0.27514 for the test and reference products, respectively (see page #063, vol. 8.1). The within subject variances in pre-albuterol PD_{20} were 0.11777 and 0.19072 for the test and reference products, respectively. The within subject variations in post-albuterol PD_{20}/pre-albuterol PD_{20} were 0.22352 and 0.31539, respectively.

2. For Inter-subject, Within-Product Variability (n=25):
The within subject variances in post-albuterol PD_{20} were 2.25197 and 1.57096 for the test and reference products, respectively (see page #064, vol. 8.1). The within subject variances in pre-albuterol PD_{20} were 1.3030 and 1.52300 for the test and reference products, respectively. The within subject variations in post-albuterol PD_{20}/pre-albuterol PD_{20} were 0.59767 and 0.40107, respectively.

III. IN VITRO STUDY:

A. Lot number, size and manufacture date:

1. Test Product

(The information reported on page #690, vol. A8.2)

Batch/Lot #6403
Theoretical Lot/Batch size: units ?
Lot size: units
Lot manufacture date (filling of canisters): July 1993
Packing Date: 8/24/93
Expiration Date: June 1995
Declared Doses: 200

Can-component Specification
(The information reported on pp. #294, 321, 352, 355; vol. A6.1)

2. Reference Listed Product
Lot #Z31383LS
Expiration Date: March 1996

B. Comparative formulations:
The following information on the drug formulations should not be released under FOI.

The following formula comparison is based on the number of doses determined from the weight of albuterol in the canister and a nominal dose ex-valve of 0.100 mg (100 µg) albuterol.

1. Reference Listed Drug

Nominal dose ex-valve:	0.100 mg (100 µg)
Weight albuterol per canister:	27.6 mg
Number of theoretical doses:	27.6/0.100=276

2. Test Product (AL Labs)

Nominal dose ex-valve: 0.100 mg (100 µg)
Weight albuterol per canister: 23.18 mg
Number of theoretical doses: 23.18/0.100=231.8

Table #1

Comparative formulations

(Weight of Ingredient per Actuation)

Ingredients	Test*	Reference**	T/R
Albuterol, USP	100 µg	100 µg	1.00
Oleic Acid, NF			
Trichloromonoflurometh ane, NF			
Dichlorodifluoromethane, NF			
Total mg/Canister***	86.28 mg	75.25 mg	1.15

* 90 µg per dose delivered to patient, approximately 10% retained on mouthpiece.

* Includes a 15.9% (16%) overage to deliver a minimum of 200 doses per canister.

* The information of the test product was provided in Volume #A1.1, page #0093 and volume #A10.1

** The information of the RLD was provided in NDA #18-473, Volume #8.1, Annual Report R-08, Section C, covering the period of 01 June 1984 to 31 May 1985.

*** Obtained by addition of the four ingredients.

Table #2
Comparative formulations
(Weight of Ingredient per Canister)

Ingredients	Test*	Reference**	T/R
Albuterol, USP	23.18 mg	27.6 mg	0.84
Oleic Acid, NF			
Trichloromonofluromethane, NF (Propellant 11)			
Dichlorodifluoromethane, NF (Propellant 12)			
Total mg/Canister***	20000 mg	20771 mg	0.96

* 90 µg per dose delivered to patient, approximately 10% retained on mouthpiece.

* Includes a 15.9% (16%) overage to deliver a minimum of 200 doses per canister.

** The information of the RLD was provided in NDA #18-473, Volume #8.1, Annual Report R-08, Section C, covering the period of 01 June 1984 to 31 May 1985.

*** Obtained by addition of the four ingredients.

Table #3
Comparative formulations
(Weight of Ingredient per %)

Ingredients	Test Prod. Theoretical Content per shot*	Test Prod. Quantity as % of Total**	Reference Prod. Quantity as % of Total***
Albuterol, USP	100 µg	0.1159%	o.1329%
Oleic Acid, NF			
Trichloromonofluro-methane, NF			
Dichlorodifluoro-methane, NF			
Total	86.28 mg	100.00%	100.00%

*90 µg per dose delivered to patient, approximately 10% retained on mouthpiece.

** The formulation of the test product provided in ANDA #73-045, volume #1.1, page #0093.

***The formulation of the RLD was provided in NDA #18-473, volume #8.1, Annual Report R-08, Section C, covering the period of June 01, 1984 to May 31, 1985.

Comments on the formulation:

a. The formulation provided in volume 1.1, Section 5, p. 93, indicates an overage of 15.9% (16%). It is not clear whether the overage applies to drug only or to all ingredients.

b. The actual, theoretical batch size and the number of filled canisters manufactured are not clear in the submission.

c. The randomization process used to select test product canisters for the comparative *in vitro* bioequivalence testing, as well as for the *in vivo* bioequivalence study was not provided.

C. Particle Size:

The Divison of Bioequivalence guidance (June 27, 1989) requests particle size determination by at least two different methods, with the cascade impactor data considered as pivotal.

The firm determined the particle size by using the following methods: Cascade Impactor, Malvern Laser, and Twin Impinger.

1. Cascade Impactor

The cascade impactor apparatus (USP 23, Chapter 601) is used to determine the following:
(1) The total mass of drug released from the inhalation aerosol.
(2) The quantity of drug collected at each location of the cascade impactor device.
(3) The mass medium aerodynamic diameter (MMAD; the diameter above and below which lies 50% of mass of the particles.
(4) The geometric standard deviation (GSD).

The firm used the cascade impactor with the following specification:

Number of stages:
Atomizing chamber: USP 23 metal throat

Flow rate: 30 L/min

Assay Method

Cascade impactor data for three canisters of test product and three canisters for RLD at BME are given on pp. 565 and 567, vol. A8.2.

The results of the cascade impactor analysis for MMAD and GSD are given below:

Table #4
Mass Median Aerodynamic Diameter (MMAD)
(in microns)

Shot #	Test Product (Batch #6403)			Reference Product (Batch #Z31383LS)		
	Mean	Range	%CV	**Mean**	Range	%CV
Start 6-30 (n=3)	**2.62**	2.4-3.0	12.7	**2.32**	2.25-2.4	3.3
Middle 91-115 (n=3)	**2.55**	2.4-2.75	7.07	**2.32**	2.25-2.35	2.49
End 176-200 (n=3)	**2.58**	2.5-2.65	2.96	**2.37**	2.3-2.4	2.44

Table #5
Geometric Standard Deviation (GSD)
(in microns)

Shot #	**Test Product** (Batch #6403)			**Reference Product** (Batch #Z31383LS)		
	Mean	Range	%CV	**Mean**	Range	%CV
Start (n=3) 6-30	**2.05**	1.7-2.55	21.7	**1.72**	1.5-2.12	19.99
Middle (n=3) 91-115	**2.11**	1.63-2.52	21.3	**1.73**	1.51-2.16	21.53
End (n=3) 176-200	**2.38**	1.86-2.68	19.1	**1.74**	1.50-2.22	23.89

Table #6
Total Mass of Drug Released from the Inhalation Aerosol
(in µg)

Shot #	**Test Product** (Batch #6403)			**Reference Product** (Batch #Z31383LS)		
	Mean	Range	%CV	**Mean**	Range	%CV
Start (n=3) 6-30	**2.83**	2.48-3.27	14.23	**2.57**	2.52-2.60	1.60
Middle (n=3) 91-115	**2.92**	2.58-3.23	11.17	**2.60**	2.43-2.70	5.78
End (n=3) 176-200	**2.94**	2.23-3.36	21.09	**2.46**	2.43-2.50	1.43

Comments on Cascade Impactor:

a. The firm's 12 June 1995 *in vitro* data submission, Vol A8.2, provides particle size data by cascade impactor. Pages 565 and 567 lists amounts of drug deposited on various stages of the impactor. The firm is requested to provide complete mass data on laboratory worksheets for each of the 18 observations for test and reference products, including amount of drug on the valve, actuator, and atomizing chamber, and date each study was performed.

b. The cascade impactor is calibrated at The firm used a flow rate of USP 23 <601> specifies that the flow rate through the cascade impactor should be within 2% of that specified by the manufacturer.

c. The respirable dose and respirable fraction data based on drug less than 5.8 and 4.7 microns for each cascade impactor study were not given.

d. Percentage material balance as defined in USP 23 <601> for each cascade impactor study was not given.

2. Laser

The sampling tube dimensions are:
Diameter at base of tube: 6mm (interior); 8 mm (exterior)
Diameter at top of tube: 51mm (interior); 55 mm (exterior)
Length of tube: 45 cm
Distance from the beam: 4.5-5.5 cm
Distance above the beam: 10-20 mm

Table #7
Particle Size Delivered from the Actuator (Mouthpiece) Laser (in microns)

Shot #	**Test Product** (Batch #6403)			**Reference Product** (Batch #Z31383LS)		
	Mean	Range	%CV	**Mean**	Range	%CV
Start (n=3) 6-30	**3.27**	3.17-3.42	4.0	**2.92**	2.72-3.10	6.5
Middle (n=3) 91-115	**3.21**	3.08-3.29	3.5	**2.97**	2.97-3.19	8.0
End (n=3) 176-200	**3.21**	3.08-3.27	3.4	**2.90**	2.82-2.96	2.5

Comments on Malvern Laser:
The particle size distribution data by Laser are missing information regarding the methodology (Volume A8.2, pp. 568-605) using the vertical downpipe. If this method for sizing aerosols is a standardized, validated method, the firm needs to provide references and other relevant information. The firm needs to comment on the effect of spraying every two or five seconds, which is more frequent than the labeled interval between successive doses, on the resultant particle size distribution. In addition, explain on the effect of spraying with the canister held in a near-horizontal position rather than the labeled near-vertical position.

3. Impinger (Deposition of Emitted Dose)

The firm employed the Impinger (single stage impactor apparatus 2, USP Chapter <601> Aerosols/Physical Tests) to determine the deposition of the emitted dose. Drug deposited on on stage 2 is less than 6.4 microns. Data are expressed as the percentage of drug in stage 1 (Upper chamber) and stage 2 (the lower chamber). The equations are presented on page #613, volume #8.2.

Table #8
Particle Size Delivered from the Actuator
(% Deposition of Emitted Dose)

Deposition Stage (number of cans)	Test Product (Batch #6403)			Reference Product (Batch #Z31383LS)		
	Mean (%)	Range	%CV	Mean (%)	Range	%CV
Deposition Stage 1 (n=5)	46.01	42.23-50.54	7.9	34.13	29.78-38.88	9.8
Deposition Stage 2 (n=5)	49.03	46.89-50.37	3.0	58.40	54.46-61.91	4.7

Comment on the Impinger Study:
Regarding the twin stage impinger study (Volume A8.2, pp. 606-615), the firm should provide the amount of drug in both the upper and lower stages for each canister, and the average shot dose as determined by Method ALMS-X-K (per ALMS-2-L). In addition, the respirable fraction for each canister for the data should be provided.

D. Spray Pattern

The spray pattern and plume geometry are used to characterize the performance of the valve and actuator.

The spray pattern was determined on one spray per each of three canisters of test and RLD at each of three distances. Each can was placed in actuator and positioned, 2.5, 5.0 and 7.5 cm away and parallel to a 20 cm X 20 cm silica gel TLC spray. Single spray was fired (the canister was shaken before each spray) for each measurment. The resulting spots were viewed under UV light and the spray pattern was outlined with a pencil. Longest and shortest diameters of the spot were measured and the mean diameter was calculated.

Table #9
Spray Pattern

	Test Product (Batch #6403)				Reference Product (Batch #Z31383LS)		
		Mean	Range	%CV	**Mean**	Range	%CV
2.5 cm Spray Pattern Diameter (cm)	Shortest (3 cans)	**15**	13-18	17.6	**16**	15-17	11.9
	Longest (3 cans)	**17**	15-20	15.6	**18.3**	18-19	3.1
	Mean (3 cans, 6 shots	**16**	14.5-19	16.2	**17.2**	16.5-17.5	3.4
5.0 cm Spray Pattern Diameter (cm)	Shortest (3 cans)	**15**	14-16	6.7	**15.7**	13-18	16.1
	Longest (3 cans)	**18.7**	18-19	3.1	**16.3**	15-18	9.4
	Mean (3 cans, 6 shots)	**16.8**	16.5-17.5	3.4	**16**	14-18	12.5
7.5 cm Spray Pattern Diameter (cm)	Shortest (3 cans)	**15.7**	14-17	9.8	**16.7**	12-20	2.5
	Longest (3 cans)	**19**	18-20	5.3	**22**	21-24	7.9
	Mean (3 cans, 6 shots)	**17.3**	16.5-18	4.4	**19.3**	16.5-22	14.2

Comment on Spray Pattern:
The comparative spray pattern profiles are inadequate. Accurate measurements cannot be assured based on the photocopies provided in Volume A8.2, pp. 619-620. In the experience of the Division of Bioequivalence, spray patterns from an inhalation aerosol do not exhibit the irregular patterns shown on pp. 619-20. The firm is requested to provide photographs of the UV spots for review, along with a complete listing of the experimental procedure, including the number of actuations fired to waste between each experiment.

E. Plume Geometry:

The firm stated the following: plume geometry testing was not performed since it is believed that no quantitative data or conclusion can be made from comparative photographs of aerosol clouds. The basis of an equivalence claim is more appropriately made on desposition of the dose delivered rather than its spray pattern (see the firm's letter dated June 12, 1995).

Comments on Plume Geometry:

It should be noted that the 1989 guidance for the In Vitro portion of Bioequivalence Requirments for Albuterol MDI encourages the sponsor to submit data on plume geometry for the test and reference products to the agency, eventhough it is optional.

F. Potency

Potency is defined as the average amount of drug delivered per spray. The results are expressed as percent of labeled amount of drug delivered from the mouthpiece per spray.

Three random cans were tested. The cans were weighed and shots were sampled at the beginning (10-11), middle (100-101) and end (199-200) sprays. The loss in each canister weight was recorded.

Table #10
Potency as measured by Amount of Drug Delivered, weight loss data are also listed

	Test Product (Batch #6403)				**Reference Product** (Batch #Z31383LS)			
	Shots #	**Mean**	Range	%CV	**Mean**	Range	%CV	**Mean T/R**
Drug Delivered (µg)	Sprays 11-12 (3 cans)	**82.76**	81.06-84.35	2.0	**91.15**	89.64-91.94	1.4	**0.91**
	Sprays 100-101 (3 cans)	**93.95**	90.82-98.18	4.0	**101.98**	97.32-106.99	4.8	**0.92**
	Sprays 199-200 (3 cans)	**107.4**	106-108.75	1.3	**98.73**	96.6-99.73	1.6	**1.09**

Weight Loss (mg)	Sprays 11-12 (3 cans)	**87**	85.8-88.7	1.8	**85**	83.9-85.8	1.2	**1.02**
	Sprays 100-101 (3 cans)	**86.8**	85.4-88.4	2.0	**84.9**	82.8-86.5	2.2	**1.02**
	Sprays 199-200 (3 cans)	**86.1**	84.0-88.0	2.3	**84.4**	83.3-85.7	1.4	**1.02**

Comments on Potency Study:
The Potency section of Volume A8.2 provides comparative data for only three canisters of test and reference products, instead of the ten canisters recommended by the 1989 *In Vitro* Guidance. No conclusions can be drawn from the data of three canisters. The firm is requested to provide comparative unit spray content for ten canisters of the test and ten canisters of the reference products used in the *in vivo* bioequivalence study, determined within the expiration dating of the products. The lot number of the reference listed drug does not correspond to that of the bioequivalence lot number. The firm is requested to confirm that these data are based on Test Method ALMS-1-K.

The firm has used three cans to determine the drug potency. The 1989 guidance requests potency determination for ten test and ten reference canisters.

IV. IN VITRO DEFICIENCIES:

1. The firm's 12 June 1995 *in vitro* data submission, Vol A8.2, provides particle size data by cascade impactor. Pages 565 and 567 lists amounts of drug deposited on various stages of the impactor. The firm is requested to provide complete mass data on laboratory worksheets for each of the 18 studies for test and reference products, including amount of drug on the valve, actuator, and atomizing chamber, and date each study was performed. Please provide legible representative plots of these studies showing the computation of MMAD and GSD.

2. The cascade impactor is calibrated at The firm used a flowrate of USP 23 <601> specifies that the flowrate through the cascade impactor should be within 2% of that specified by the manufacturer. Please comment. Please state the model number of the cascade impactor.

3. Cascade impactor validation tests in Volume 7.1, "Drug Product Specifications and Tests" are dated November 1994. Do these validation data apply to the comparative data summarized in Volume A8.2, pp. 565, 567?

4. The firm is requested to provide respirable dose and respirable fraction data based on drug less than 5.8 and 4.7 microns for each cascade impactor study. These data should be computed as described in USP 23, <601>.

5. Percentage material balance as defined in USP 23 <601> should be provided for each cascade impactor study. The mass of formulation delivered and the concentration of drug in the formulation should also be provided, along with the quantities in each individual canister used to compute these average mass and concentration values.

6. Regarding the batch record, please indicate the actual and theoretical batch size, including the number of filled canisters manufactured.

7. The firm is requested to provide an explanation of the randomization process used to select test product canisters for the comparative *in vitro* bioequivalence testing, as well as for the *in vivo* bioequivalence study.

8. The formulation provided in volume 1.1, Section 5, p. 93, indicates an overage of 15.9% (16%). Please clarify whether the overage applies to drug only or to all ingredients. If to all ingredients, does the product include an additional overage of drug only?

9. The Potency section of Volume A8.2 provides comparative data for only three canisters of test and reference products, instead of the ten canisters recommended by the 1989 *In Vitro* Guidance. In addition to estimation of mean drug delivery at beginning, middle and end of canister life, these ten canister data are also used to assure conformity to uniformity of unit spray content specifications (USP <905>). No conclusions can be drawn from the data of three canisters. The firm is requested to provide comparative unit spray content for ten canisters of the test and ten canisters of the reference products used in the *in vivo* bioequivalence study, determined within the expiration dating of the products. The lot number of the reference listed drug does not correspond to that of the bioequivalence lot number. The firm is requested to confirm that these data were based on Test Method ALMS-1-K.

10. Comparative spray pattern profiles are inadequate. Accurate measurements cannot be assured based on the photocopies

provided in Volume A8.2, pp. 619-620. In the experience of the Division of Bioequivalence, spray patterns from an inhalation aerosol do not exhibit the irregular patterns shown on pp. 619-20. The firm is requested to provide photographs of the UV spots for review, along with a complete listing of the experimental procedure, including the number of actuations fired to waste between each experiment.

11. Regarding the particle size distribution data by Laser, please provide information regarding the methodology (Volume A8.2, pp. 568-605) using the vertical downpipe. If this method for sizing aerosols is a standardized, validated method, please provide references and other relevant information. Please comment on the effect of spraying every two or five seconds, which is more frequent than the labeled interval between successive doses, on the resultant particle size distribution. Please comment on the effect of spraying with the canister held in a near-horizontal position rather than the labeled near-vertical position.

12. Regarding the twin stage impinger study (Volume A8.2, pp. 606-615), please provide the amount of drug in both the upper and lower stages for each canister, and the average shot dose as determined by Method ALMS-X-K (per ALMS-2-L). In addition, please provide respirable fraction for each canister for the data tabulated on p. 615, as defined in USP 23, <601), Single-stage Impactor Apparatus 2.

13. The firm is advised that review of *in vitro* data is ongoing and additional questions may arise pending completion of this review.

V. **Issues need to be answered for making the decision:**

1. Regarding Statistiacl Issues

   a. The number of days between treatments were different from one subject to another. The highest range was 48 days and lowest range was 2 days between two successive visits. It is clear from the study, some treatments were done at longer intervals as compared to others. The question is: Do longer intervals have an effect on the outcome of the statstical analysis?

   b. An issue has been raised that deals with residual effects (i.e. carry over effects). Should the possibility of residual effects such as the case of blood level concentration be considered in the evaluation of MDI drugs?

VI. **RECOMMENDATION:**
At the present time the 1994 guidance does not specify the conference interval range value for Albuterol MDI. The status of approval of Albuterol should based solely on the outcome of the medical and safety evaluation (Division of Pulmonary Drug Products, HFD-570), the statistical analysis (Division of Biometrics, HFD-700) and the firm's response to the in vitro deficiencies that are identified above. The firm should be informed of the deficiencies cited above (the in vitro deficiencies #1-13)).

Zakaria Z. Wahba, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALED RMHATRE 7/16/96
FT INITIALED RMHATRE

Concur: _____ Date: 7/17/96
Keith K. Chan, Ph.D.
Director
Division of Bioequivalence

cc: ANDA 73-045 (original, duplicate), HFD-600 (Hare), HFD-630, HFD-658 (Mhatre, Wahba), Drug File, Division File
ZZWahba/030796/032596/061096/070596/071596/file #73045s.695

APR 18 1989

Albuterol
90 mcg inhalation aerosol
ANDA #73-045
Reviewer: Marilyn N. Martinez
Wang #6127f

Superpharm Corporation
Bayshore, New York
Submission dated:
December 23, 1988

REVIEW OF A PROTOCOL AND IN-VITRO DATA

OBJECTIVE:

The firm has submitted the following data for review:

a. the bioequivalence protocol for an ongoing clinical study. The firm states that this protocol has been informally reviewed by the Food and Drug Administration and has been revised to include Agency suggestions.

b. in-vitro data for the two production batches of the proposed drug product, Albuterol Aerosol Inhaler, 90 mcg, and one batch each of the listed products, Proventil Inhaler (Schering) and Ventolin Inhaler (Glaxo).

c. comparative spray pattern study.

It should be noted that Superpharm Corporation is authorized to act as the U.S. agent on behalf of Generics (UK) Limited in all matters pertaining to this ANDA. Superpharm Corporation will function as the U.S. contact/liason between Generics (UK) Limited and the FDA both prior to and subsequent to product approval.

PROTOCOL:

TITLE: Comparative 3-way double-blind, randomized, clinical efficacy study between albuterol (Generics (U.K.) Ltd.) and Proventil (Schering) and Ventolin (Glaxo) 90 mcg metered dose albuterol inhalers.

DESIGN: randomized, 3-way, double blind clinical trial using the double dummy technique for subject and technician blinding.

BLINDING TECHNIQUE: on each of the three study days, each patient will inhale 2 puffs of an active aerosol and 2 puffs of the other two placebo aerosols. All three will be sequentially inhaled at 30-second intervals. The actuator sequence will be consistent across study days for any given study subject.

A sample subject dosing schedule is defined as follows:

	ALBUTEROL	VENTOLIN	PROVENTIL
DAY 1	ACTIVE	PLACEBO	PLACEBO
DAY 2	PLACEBO	ACTIVE	PLACEBO
DAY 3	PLACEBO	PLACEBO	ACTIVE

Neither the patients nor the technicians performing the tests will know the identity of the respective canisters.

DOSE: 180 mcg (2 puffs)

SUBJECTS: 60 male and female volunteers, ages 18-60 years, presenting with uncomplicated stable asthma will be employed in the study. Patients will be selected on the basis of a typical history of asthma and the prior observation of an increase in FEV_1 of at least 15% that of control values. Patients will be studied on three different days, 2 to 7 days apart.

Subjects are permitted to take their chronic asthma medications. However, they must refrain from taking the following preparations in accordance to the indicated washout schedule:

.inhaled beta-adrenergic agonist	at least 8 hours
.oral beta-adrenergic agonist	at least 12 hours
.lung inhaled cromolyn sodium	at least 30 days
.antihistamines	at least 48 hours
.hydroxyzine	at least 96 hours
.xanthines a) taken bid	at least 24 hours
b) taken q24h	at least 48 hours
.calcium channel blockers	at least 48 hours
.beta blockers	at least 24 hours
.anticholinergic eye drops	at least 24 hours
.alpha-adrenergic agonist	at least 12 hours
.aspirin and non-steroidal anti-inflammatory drugs	at least 7 days

Patients on stable doses of systemic or aerosol steroids will not be excluded and the steroids will be maintained at the same dose during the study.

INCLUSION CRITERIA:

- .nonsmokers for at least 6 months prior to the study
- .males and nonpregnanat females who are 18-60 years of age and who are within ±10% of the ideal weight for their height, age and gender (Metropolitan Life Insurance Bulletin, 1983)
- .mild to moderate chronic asthmatics (FEV_1 = 50-85% of predicted

EXCLUSION CRITERIA:

- .history of cardiovascular, renal, neurologic, liver or endocrine disease
- .intolerance to aerosolized $beta_2$-adrenergic agonists
- .history of hypersensitivity to any of the ingredients of the metered dose inhalers
- .evidence of respiratory tract infection within 6 weeks prior to the study
- .history of status asthmaticus, cystic fibrosis or bronchiectasis
- .inability to tolerate the temporary withdrawal of current asthma medication

RESTRICTIONS:

- .use of caffeine-containing foods and beverages must be prohibited at least 12 hours prior to and throughout the study
- .subjects should be instructed to refrain both from lying down or engaging in strenuous exercise throughout the 6 hour test period

BASELINE MEASUREMENTS:

Verification that the FEV_1 predose is within $\pm$15% the of baseline value between study days. If the FEV_1 is not within $\pm$15%, the patient will be rescheduled for another day or excluded from the investigation.

STUDY DAY PROCEDURES:

Electronic spirometer attached to a fast response X-Y plotter and to a timer for the measurement of FEV_1.

On each day, maximum expiratory flow volume curves and FEV_1 will be obtained in triplicate before and after the administration of the consecutive three types of aerosols (one active plus two placebos) at 5, 15, 30, 60, 90, 120, 180, 240, 300 ands 360 minutes. Predose FEV_1 will be done at the same time in the morning for each suject throughout the study. The data will be reduced and analyzed as forced vital capacity (FVC) and FEV_1. The maximum expiratory flow-volume curves will be performed on consecutive maneuvers, superimposing one curve over the other without removing the mouthpiece to insure measurement reproducibility.

Respiratory rate, pulse rate and blood pressure will be taken immediately before each pulmonary function measurement. A 12- lead ECG will be done 60 minutes post-dose.

STATISTICAL ANALYSIS:

The treatments will be compared in pairwise fashion using an ANOVA. The statistical model will include the error due to sequence, treatment and the 11 levels of TIME FACTOR (repeated measures). For the drug main effect and the drug X TIME FACTOR interaction, the Westlake 95% symmetrical confidence limits of clinical equivalence around the standard treatment (Ventolin or Proventil) will be established. The confidence limits will be expressed as a percentage of the standard treatment for a pulmonary response measure.

IN-VITRO TEST PROCEDURES

Various in-vitro tests were performed at regular intervals over a period of serveral months for two differeng production batches of cans. In addition, one batch of Proventil and one batch of Ventolin canisters were tested both under ambient room temperature and accelerated 40° C/75% relative humitidity conditions. The batch of the Superpharm albuterol aerosol (Lot # 0291E1) and the Proventil and Ventolin inhalers (Lot #'s 7BBS460 and Z12927NA respectively) are the same batches currently being used in the ongoing clinical trial.

The following in-vitro data is being submitted for Agency review:

a) content weight
b) can content
c) shot weight
d) shot dose
e) particle size

The definition of each of these terms are indicated in the Appendix of this review.

COMMENTS:

1. The data submitted for the in-vitro characterization of the Superpharm albuterol inhalation aerosols are currently under review. The results of this evaluation will be forwarded to the firm in a separated letter.

2. The recommended protocol for the clinical trial of generic albuterol and metaproterenol inhalation aerosols have been revised. The firm is therefore advised to incorporate the following changes into the in-vivo portion of their bioequivalence submission:

   a. the current guidance recommends the evaluation of 2 dosage levels per product (1 and 2 puffs of albuterol, equivalent to 90 mcg and 180 mcg per dose respectively). The study design submitted by Generics, LTD. includes only one dosage level per product (2 puffs albuterol, equivalent to 180 mcg per dose). To correct this discrepancy, the firm is advised to conduct a supplemental three treatment randomized crossover clinical trial. This study should employ 40 asthmatic subjects who will receive a 90 mcg (1 puff) dose of albuterol. The data generated from the ongoing clinical trial will provide the necessary comparison between the clinical response to 2 puffs of the Generic's LTD albuterol vs that of 2 puffs of Proventil or Ventolin.

ONE PUFF STUDY PROTOCOL

With the exception of the following revisions, the firm may use a protocol similar to that employed in the two puff study:

1. the inclusion and exclusion criteria indicated by the firm, are acceptable with the following revisions:

   a) subjects should not have received an investigational drug within 30 days prior to the current study
   b) subjects must not be currently taking oral corticosteroids

   In addition, the recommended drug washout should include the following criteria:

a) inhaled corticosteroids	at least 30 days
b) anticholinergics	at least 7

2. the study population should include 8 subjects presenting with an FEV_1 of 40-60% of predicted and 32 subjects with FEV_1 of 60-80% of predicted. The severity of the disease condition should be established under drug washout conditions (see Appendix 2 of the Division Albuterol Guidance dated February 9, 1989).

3. the firm has indicated that it is currently using the double dummy technique for blinding of subjects and technical support staff. The firm may wish to consider canister camouflag in their supplemental study.

4. the firm is advised to refer to the Division of Bioequivalence Guidance for In-Vivo Bioequivalence Studies of Metaproterenol Sulfate and Albuterol Inhalation Aerosols (Metered Dose Inhalers), dated February 9, 1989, for more details regarding the recommended in-vivo test procedures and the corresponding method of data analysis.

b. both for the one puff and two puff data sets, the following data evaluation procedures are recommended:

1. for each treatment group, the following information should be included in the final study report (individual subject data and related statistics:

   a) onset of the therapeutic response
   b) duration of the therapeutic response
   c) AUC calculated from the onset of the response to hour 3
   d) AUC calculated from the onset of the repsonse to the time of corresponding with the termination of the response
   e) $FEV_{1\ max}$ (the peak bronchodilatory response
   f) TMAX
   g) FEV_1 values at all measurement times within each evaluation period

   For additional details regarding these parameters, refer to the aforementioned Division Guidance.

2. the firm should statistically compare the therapeutic efficacy of the three products at each of the two dosing levels using a three-way ANOVA which includes the error attributable to subjects(seq), period, treatment and compares the effect of sequence as a between-subject error term. All three treatments should be compared simultaneously. However, the data for the two dosing levels SHOULD NOT BE POOLED. Separate statistical evaluation should be performed for the data generated with one puff and two puffs.

   Pairwise comparisons for each parameter should include the determination of the 90% confidence intervals around the difference between any 2 products relative to some reference mean (Proventil or Ventolin). Generics LTD may also wish to include the profile analysis described in their current submission.

c. the data generated in accordance with the original Generic LTD protocol will be used for comparing the clinical efficacy of 2 puffs of the Generics's albuterol canister against that effected by 2 puffs of Ventolin or Proventil. However, the following subjects should be dropped from the study:

   1. subjects whose dose of systemic corticosteroids changed during the course of the study period

   2. asthmatics whose predose FEV_1 exceeds 80% of predicted.

To accomodate other differences between the firm's study design versus that currently recommended by the Division of Bioequivalence, the firm is requested to submit 2 sets of data analysis:

1. including all study subjects
2. omitting those subjects who do not meet the exclusion and inclusion criteria listed in the Division of Bioequivalence study Guidance, dated February 9, 1989.

If subject selection has not as yet been completed, the firm is requested to recruit several patients whose predose FEV_1 is within the range of 40-60% of predicted. In addition, for all study subjects, the firm is should delineate those patients whose predose FEV_1 fall within 40-60% of predicted and those which are 60-80% of predicted.

RECOMMENDATIONS:

The protocol for a proposed bioavailability study comparing the test product with Proventil (Schering) and Ventolin (Glaxo) is acceptable provided that the firm incorporated the comments in the protocol.

The firm should be informed of the above Recommendations and Comments.

Marilyn N. Martinez, Ph.D.
Division of Bioequivalence
Review Branch II

RD INITIALED FPELSOR
FT INITIALED FPELSOR

Concur: _____ Date: 4/17/89.
S.V. Dighe Ph.D.
Director, Division of Bioequivalence

MNMartinez/MNM/04-17-89/Wang #6127f

cc. ANDA #73-045 original, HFD-230, HFD-200 (Hare), HFD-22 (Hooton), HFD-255 (Martinez, Pelsor), Drug File

DIV FILE

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF GENERIC DRUGS

DATE: 4 March 1997

TO: Rabindra N. Patnaik, Ph.D.
Acting Director
Division of Bioequivalence

THROUGH: Shriniwas G. Nerurkar, Ph.D.
Team Leader, Branch II
Division of Bioequivalence

3/4/1997

THROUGH: Ramakant M. Mhatre, Ph.D.
Team Leader, Branch III
Division of Bioequivalence

3/4/97

FROM: Wallace P. Adams, Ph.D. WP Adams
Office of Generic Drugs

and

Gur Jai Pal Singh, Ph.D.
Branch II
Division of Bioequivalence

SUBJECT: Content Uniformity:
Alpharma Albuterol MDI (ANDA 73-045)

I. BACKGROUND

The 27 June 1989 Division of Bioequivalence *Guidance for the In Vitro Portion of Bioequivalence Requirements for Metaproterenol Sulfate and Albuterol Inhalation Aerosols (Metered Dose Inhalers)* recommends "potency" testing of ten canisters each of test and RLD products at beginning, middle and end of canisters through-life. The guidance does not establish specifications for acceptable data. A USP Content Uniformity test for MDI's became official on 15 Nov 1992. In the reviewers' opinion, this test established the specifications for the "potency" test recommended in the DBE guidance.

Alpharma's ANDA 73-045 was submitted on 23 December 1988. In 1989 and 1990, *in vivo* bioequivalence studies were submitted to the ANDA. These studies were not conducted with a study design capable of establishing bioequivalence. On 14 February 1994, the firm submitted IND for a methacholine challenge bioequivalence study. This *in vivo* bronchoprovocation study, submitted 12 and 22 June 1995, has met the established bioequivalence interval of 67 - 150%. The *in vitro* "potency" (content uniformity) data accompanying the *in vivo* study,

conducted on the test and RLD bio batches, was unacceptable. Initial "potency" data were based on only three canisters of test and three canisters of RLD. In addition, the firm failed to validate its analytical method, and used a nonstandard unit spray collecting device that initially failed methods validation when tested by FDA's Division of Drug Analysis.

The first and only comparative content uniformity data which the firm has provided for 10 canisters, using a validated analytical method, was submitted on 6 January 1997 (Volume 13.1). These data were provided for test product batch # 8457 and Ventolin MDI batch # 6ZP0756. These nonbio batches were within expiry dating when tested. The test product batch size was .theoretical), and (number of units filled), which meets the Division of Bioequivalence *in vitro* guidance recommendation of a minimum batch size of 5,000 canisters.

Through-life (beginning, middle, and end) content uniformity data for test product batch # 8457 revealed low drug delivery at middle of the canister. USP <905> states that, unless otherwise specified in the individual monograph, at level 1 (10 dosage units, i.e., the number of sprays defined in the labeling as the recommended dose), no more than 1 dosage unit lies outside of 75.0 - 125.0%. Of 30 dosage units tested, no more than 3 lie outside of 75 - 125%. Of the ten canisters tested from batch # 8457, three dosage units, one from each of three canisters, were below 75% of label claim. All three dosage units which delivered less than 75% of the drug occurred at the middle of through-life testing. The nonrandom occurrence of the low dosage units suggests that drug delivery is potentially low at the middle of canister dosing. This observation was not observed for the Ventolin MDI product in the Alpharma testing. Neither was it observed for test or RLD testing for any of the three approved ANDA products. Further study is warranted.

II. CONTENT UNIFORMITY DATA COMPARISON (Mcg/Actuation)

	TEST			REFERENCE		
	Mean*	Range	%CV	Mean*	Range	%CV
Alpharma		**Lot # 8457**			**Lot # 6ZP0756**	
Beg	86.1	69.9-97.8	10.4	78.8	73.7-85.0	2.0
Mid	75.7	61.5-89.6**	12.8	82.5	78.3-87.4	1.1
End	86.7	70.2-109.5	13.3	87.3	80.8-91.6	1.5
Armstrong		**Lot # 024-4**			**Lot # Z30513ES**	
Beg	90.6	82.7-97.6	5.6	94.4	90.5-97.4	2.3
Mid	91.7	83.5-98.6	4.5	95.5	90.5-101.7	3.6
End	99.4	93.5-109.7	4.5	100.2	94.6-103.7	3.1
IVAX		**Lot # 92047**			**Lot # Z30402CS**	
Beg	85.1	75.4-98.3	9.3	85.3	74.5-92.2	6.0
Mid	90.8	80.9-104.3	9.1	84.3	66.2-92.5***	9.0
End	93.1	76.0-109.8	12.3	92.2	87.1-98.2	4.1
Medisol		**Lot # 801-0008**			**Lot # Z30292BS**	
Beg	82.4	74.3-87.1	4.9	91.7	88.6-95.9	3.0
Mid	88.6	79.0-95.8	6.3	93.0	83.4-100.9	5.4
End	94.6	87.9-102.2	4.9	99.5	93.4-110.1	5.6

* Mean of 10 dosage units, one from each of 10 canisters, and each dosage unit consisting of two actuations

** Three dosage units at middle canister testing delivered less than 75.0 but more than 65.0% of drug: 62.1, 61.5 and 65.9 mcg/actuation

*** One dosage unit delivered less than 75.0% but more than 65.0% of drug: 66.2 mcg/actuation

III. COMMENTS

Section II above summarizes content uniformity data for the Alpharma product currently under review in the Division of Bioequivalence, as well as the acceptable content uniformity data submitted with the three previously approved Albuterol MDI applications. Complete testing results for 10 dosage units from test and RLD products for the four ANDA's is attached to this memorandum.

The reviewers have the following comments:

1. Content uniformity data for test product lot # 8457 differ from the comparative content uniformity data for Ventolin MDI, lot # 6ZP0756. Moreover, the data differ from that submitted in support of the three approved ANDA's, both for the test and RLD products. Three lot # 8457 dosage units delivered less than 75.0% of labeled drug. All three low dosage units occurred at middle canister testing, rather than randomly distributed over beginning, middle and end of the canister. The 10 dosage unit mean drug delivery was low at the middle testing, 75.7 mcg/actuation, compared to 86-87 mcg/actuation at the beginning and end.

2. The low drug delivery at middle of canister testing was not observed in the cascade impactor (CI) testing. The CI studies involve different testing methodology than used for content uniformity testing. CI testing required firing 15 actuations into the CI, whereas the content uniformity testing involved two actuations from each of ten canisters. Drug delivery out of the actuator (ex-actuator) for the test product at beginning, middle and end, from the CI studies for lot # 8457 was 98.1, 94.9 and 106.2 mcg/actuation.

3. Content uniformity testing, as described by USP <905>, is somewhat ambiguous regarding whether each dosage unit (the number of sprays defined in the labeling as the recommended dose) is obtained from a separate MDI canister (i.e., intercanister testing), whether multiple dosage units may be obtained from the same canister (intracanister testing), or whether testing may be a combination of both intra- and intercanister testing is acceptable. The reviewers believe that intercanister testing is intended.

4. Unlike the ambiguity of the USP Content Uniformity test (Comment # 3 above), the 1989 Division of Bioequivalence *in vitro* guidance specifically states that "potency" testing is to be conducted on ten test and ten RLD canisters. Through-life testing (beginning, middle, and end) is to be conducted on two actuation data. Note that this guidance was issued prior to the content uniformity testing for MDI's in the USP.

5. Although ANDA 73-045 was submitted prior to issuance of either the Division of Bioequivalence *in vitro* guidance or the USP <905> Content Uniformity requirements for MDI's, the firm's Content Uniformity testing method and specifications follow USP <905>. See regulatory specification in Chemist's Review No. 8, and the Certificate of Analysis for batch # 8457, Vol. 11.1, p. 94. The firm's Method GS049 and ALMS-6-K specify

conducting the Content Uniformity test on 10 canisters at beginning (actuations 12-13).

6. The "potency" test recommended in the Division of Bioequivalence guidance is designed to assure comparability of drug delivery at beginning, middle and end of canister life. The firm's data suggest that the performance of the test batch at the middle of the canister is different from the beginning and end of the canister, and also different from the RLD. In addition to the three low dosage units at middle testing, the intercanister variability of the test product is greater at beginning, middle and end than that of the RLD.

7. A concentration effect has been reported for rapidly flocculating and creaming suspensions, resulting in increased drug delivery through life. Examination of the mean drug delivery data of Section II reveals such an effect. In all cases for the RLD, mean delivery at the end of the canister was greater than at the beginning. This was also true of the three approved test products. In most cases, the mean increase was progressive, from beginning to middle to end. The only apparent exception to this concentration effect is the Alpharma test product. Note that the Alpharma product uses a valve and a actuator, whereas the Armstrong, IVAX, and Medisol products all use a valve and a actuator. An examination of the mechanical design of each valve may suggest whether differences in drug delivery through-life might be anticipated.

8. Reviews of the three approved ANDA's for albuterol MDI stated that the test products met the requirements of USP <905> Content Uniformity testing. The reviews did not specifically state that the requirements were met at beginning, middle and end, although this is the case.

9. Because drug delivery may change progressively through canister life, the Division of Bioequivalence believes that, as a bioequivalence criterion, a test product should meet USP <905> Content Uniformity requirements at beginning, middle and end of canister through-life. Therefore, the firm is requested to provide the following:

   a. Content uniformity data on 30 canisters of test lot # 8457 at beginning, middle and end.

   b. Content uniformity data on 10 canisters of test lots # 8671 and 8834 at beginning, middle and end. For each batch, if 10 canisters fail to meet the USP specification at each of beginning, middle and end, an additional 20 canisters should be tested as stated in USP <905>. Note that, consistent with the 27 June 1989 Division of Bioequivalence *Guidance for the In Vitro Portion of Bioequivalence Requirements for Metaproterenol Sulfate and Albuterol Inhalation Aerosols (Metered Dose Inhalers)*, the specifications will be evaluated separately at beginning, middle and end of canister through life.

   c. Data may be provided in the same format as that on pages 430 and 431 of the 6 January 1997 submission.

10. Additional information is also requested by the Division of Bioequivalence:

    a. The specific model of cascade impactor used by the firm for the data submitted on 6 January 1997.

    b. The expiration dates for test product batches # 8671 and 8834.

    c. Testing dates for the twin impinger data submitted on 12 June 1995 and 27 July 1996.

    d. Conduct of the Microscopy Test (USP <601>) on canisters from test product batches # 8457, 8671, and 8834, and Ventolin MDI batch # 6ZP0756. The Division requests these comparative baseline data, noting that the test serves a number of purposes: determination of the number of particles larger than 10 microns; identification of unusual agglomeration; characterization of crystal morphology; and identification of foreign particulates not related to the drug substance.

The firm should be advised of Comments # 9 and 10 only.

cc: ANDA #73-045, (original, duplicate), Adams (HFD-600), Mhatre (HFD-658), Patnaik (HFD-650), Singh (HFD-655), Nerurkar (HFD-655), Drug File, Division File

ALPHARMA
73-045
VOL 13.1

NON BIO BATCH

Average Drug Delivered and Average Weight Loss per Spray

Albuterol Inhalation Aerosol, Batch # 8457

	Average Drug Delivered (ug/spray)						Average Weight Loss (mg/spray)					
	Sprays 11-12	Sprays 100-101	Sprays 199-200	Mean	Range	RSD (%)	Sprays 11-12	Sprays 100-101	Sprays 199-200	Mean	Range	RSD (%)
Can #1	93.0	84.2	70.2	82.5	70.2-93.0	13.9	90.0	87.9	88.7	88.9	87.9-90.0	1.2
Can #2	97.8	62.1	97.8	85.9	62.1-97.8	24.0	94.0	88.0	87.6	90.0	87.6-94.0	4.0
Can #3	81.9	61.5	88.6	77.3	61.5-88.6	18.3	90.0	86.7	87.0	87.9	86.7-90.0	2.1
Can #4	86.4	89.6	109.5	95.2	86.4-109.5	13.2	89.8	87.6	87.2	88.2	87.2-89.8	1.6
Can #5	96.2	83.3	84.1	87.9	83.3-96.2	8.2	88.9	87.1	88.2	88.1	87.1-88.9	1.0
Can #6	88.6	76.9	93.4	86.3	76.9-93.4	9.8	89.1	87.5	86.8	87.8	86.8-89.1	1.3
Can #7	86.8	78.0	85.4	83.4	78.0-86.8	5.7	88.3	86.0	87.0	87.1	86.0-88.3	1.3
Can #8	86.3	65.9	85.7	79.3	65.9-86.3	14.6	88.1	85.2	84.3	85.9	84.3-88.1	2.3
Can #9	73.9	74.4	73.7	74.0	73.7-74.4	0.5	89.8	87.5	86.7	88.0	86.7-89.8	1.8
Can #10	69.9	81.4	79.0	76.8	69.9-81.4	7.9	87.7	85.8	85.5	86.3	85.5-87.7	1.4
Mean	86.1	75.7	86.7				90.0	86.9	86.9			
Range	69.9-97.8	61.5-89.6	70.2-109.5				87.7-94.0	85.2-88.0	84.3-88.7			
RSD (%)	10.4	12.8	13.3				2.0	1.1	1.5			

Overall mean = 82.9 ug/spray % RSD = 13.3

Average Drug Delivered per Spray	
# of results within 75.0 - 125.0% of claim (90 ug/spray) (i.e., 67.5 to 112.5 ug/spray)	27
# of results outside 75.0 - 125.0% of claim, but within 65.0 - 135.0% of claim (90 ug/spray) (i.e., 58.5 to 121.5 ug/spray)	3

430

BIO BATCHES: TEST - LOT # 6/02

ALPHARMA
73-045

Potency

Average Drug Delivered and Average Weight Loss per Spray

Ventolin Inhalation Aerosol, Lot 6ZP0756, Exp. 04/99

	Average Drug Delivered (ug/spray)						Average Weight Loss (mg/spray)					
	Sprays 11-12	Sprays 100-101	Sprays 199-200	Mean	Range	RSD (%)	Sprays 11-12	Sprays 100-101	Sprays 199-200	Mean	Range	RSD (%)
Can #1	82.1	78.3	89.6	83.3	78.3-89.6	6.9	85.8	83.4	84.5	84.6	83.4-85.8	1.4
Can #2	85.0	87.4	93.3	88.6	85.0-93.3	4.8	87.5	86.7	86.8	87.0	86.7-87.5	0.5
Can #3	81.4	85.1	90.1	85.0	81.4-88.6	4.2	86.1	85.5	84.5	85.4	84.5-86.1	0.9
Can #4	76.5	84.5	86.7	82.6	76.5-86.7	6.5	82.8	80.8	81.2	81.6	80.8-82.8	1.3
Can #5	85.0	81.4	91.6	86.0	81.4-91.6	6.0	87.4	85.5	86.4	86.4	85.5-87.4	1.1
Can #6	74.0	79.5	80.8	78.1	74.0-80.8	4.6	83.5	81.7	83.0	82.7	81.7-83.5	1.1
Can #7	73.7	82.5	85.6	80.6	73.7-85.6	7.7	83.6	82.2	82.2	82.7	82.2-83.6	1.0
Can #8	75.0	80.7	81.6	78.5	75.0-80.6	3.9	85.6	84.0	83.2	84.3	83.2-85.6	1.5
Can #9	77.8	84.4	87.0	83.1	77.8-87.0	5.7	84.9	84.0	84.8	84.6	84.0-84.9	0.6
Can #10	77.7	81.6	86.6	82.0	77.7-86.6	5.4	84.6	84.2	84.7	84.5	84.2-84.7	0.3
Mean	78.8	82.5	87.3				85.2	83.8	84.1			
Range	73.7-85.0	78.3-87.4	80.8-91.6				82.8-87.5	80.8-86.7	81.2-86.8			
RSD (%)	5.4	3.4	4.6				1.9	2.2	2.1			

Overall mean = 82.9 ug/spray % RSD = 6.1

Average Drug Delivered per Spray	
# of results within 75.0 - 125.0% of claim (90 ug/spray)(i.e., 67.5-112.5 ug/spray)	30
# of results outside 75.0 - 125.0% of claim, but within 65.0 - 135.0% of claim (90 ug/spray)(i.e., 58.5-121.5 ug/spray)	0

ARMSTRONG
ANDA 72-273

10/18/94

Albuterol Test Result Summary
INVITRO BIOEQUIVALENCE STUDY

Summary Alb 024-4

ARMSTRONG

Product: Albuterol
Lot#: 024-4

	Specifications	SOP	Actuator Station	mean	N	RSD %	STD DEV %	Unit # 1	2	3	4	5	6	7	8	9	10
								BF65.99	PK61.81	BF005-BF3	PK61.76	PK61.78	JL66 80	PK61.80	BF65.97	BF65.98	PK61.74
Unit Spray Test(µg/Spray)	90 ± 22.5 µg	ALB-004	overall	93.9		6.33	5.94	(97.55)	97.39	93.50	91.68	90.97	(82.68)	93.12	85.40	86.70	86.84
			Beginning	90.6	10	5.58	5.05	91.08	98.57	93.10	90.59	83.52	91.96	91.43	90.15	96.77	89.71
			Middle	91.7		4.45	4.08	100.44	109.65	93.50	102.69	98.12	99.01	98.21	94.50	98.29	99.91
			End	99.4		4.50	4.48										
Number of Spray	≥200	ALB-004		220+	10	0.19	0.42	220+	220+	220+	220+	220+	220+	219+	220+	220+	219+
Shot Weight (mg)	87 ± 10	ALB-004		83.3	10	0.75	0.63	83.38	82.93	82.37	82.74	84.09	83.14	84.20	82.78	84.00	83.37
								JA167.57	JA167.58	JA167.59							
Cascade Impaction RI (Respirable Fraction)	≥20%	DRG-005	overall	55.3	9	5.04	2.79										
			Beginning	56.6	3	4.36	2.47	58.7	53.9	57.3							
			Middle	52.7		3.43	1.81	54.6	51.0	52.5							
			End	56.5		4.54	2.57	57.2	53.7	58.7							
MMAD	<5	DRG-005	overall	2.6	9	3.12	0.08										
			Beginning	2.58	3	3.77	0.10	2.47	2.66	2.60							
			Middle	2.67		3.39	0.09	2.59	2.77	2.66							
			End	2.58		0.45	0.01	2.57	2.59	2.59							
Sigma G	<2	DRG-005	overall	1.5	9	1.90	0.03										
			Beginning	1.49	3	1.69	0.03	1.49	1.52	1.47							
			Middle	1.48		1.40	0.02	1.46	1.50	1.49							
			End	1.51		2.76	0.04	1.52	1.54	1.46							
								JA167.61	JA167.62	JA167.63							
Microscopy (particle size)	%>5 µm	DRG-007		0.02%	3	173.21	0.00	0.05%	0.00%	0.00%							
	%>10 µm			0.00%		#DIV/0!	0.00	0.00%	0.00%	0.00%							
	%>20 µm			0.00%		#DIV/0!	0.00	0.00%	0.00%	0.00%							
								CYG64.71	CYG64.72	CYG64.73							
Spray Pattern	2.5 cm	ALB-006	Shape		3			passes	passes	passes							
	5.0 cm		Shape					passes	passes	passes							
	7.5 cm		Size < 3 cm					passes	passes	passes							
			Shape					passes	passes	passes							

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Checked by CDERR

ARMSTRONG
ANDA 72-273

Albuterol Test Result Summary
INVITRO BIOEQUIVALENCE STUDY

Product: Ventolin
Lot#: Z30513ES, exp 9/95

	Specifications	SOP	Actuator Station	mean	n	RSD %	STD DEV %	Unit # 1	2	3	4	5	6	7	8	9	10
								PK41.75	PK41.77	HF45.100	PK41.79	ALN001.HF.1	ALN001.HF.1	PK41.80	PK41.81	JL44.31	JL44.31
Unit Spray Test(µg/Spray)	90 ± 22.5 µg	ALB-004	overall	96.7	10	3.95	3.82										
			Beginning	94.4		2.20	2.15	93.53	95.03	90.49	96.39	93.54	93.15	97.29	93.52	97.36	93.41
			Middle	95.5		3.60	3.43	95.42	97.30	90.53	94.11	97.08	91.07	98.76	95.73	101.71	92.13
			End	100.2		3.08	3.08	102.25	98.84	96.42	98.68	102.16	99.21	103.14	103.65	94.57	102.64
Number of Spray	≥200	ALB-004		206	10	1.27	2.62	202	206	210	208	208	205	204	209	204	204
Shot Weight (mg)	87 ± 10	ALB-004		88.2	10	1.61	1.42	89.28	87.76	85.62	88.11	87.97	90.04	87.57	86.76	89.48	89.81
								EV72.13	EV72.14	EV72.18							
Cascade Impaction RF (Respirable Fraction)	≥20%	DRG-005	overall	49.6	9	11.26	5.59										
			Beginning	48.4	3	13.96	6.76	52.1	40.6	52.5							
			Middle	52.9		13.29	7.03	55.7	44.9	58.1							
			End	47.6		4.92	2.35	50.2	47.1	45.6							
MMAD	<5	DRG-005	overall	2.6	9	2.71	0.07										
			Beginning	2.60	3	3.90	0.10	2.62	2.49	2.69							
			Middle	2.63		2.16	0.06	2.61	2.58	2.69							
			End	2.67		1.92	0.05	2.66	2.63	2.73							
Sigma G	<2	DRG-005	overall	1.4	9	1.24	0.02										
			Beginning	1.43	3	0.70	0.01	1.42	1.43	1.44							
			Middle	1.44		1.06	0.02	1.43	1.44	1.46							
			End	1.45		1.59	0.02	1.44	1.44	1.48							
								EV72.32									
Microscopy (particle size)	%>5 µm	DRG-007		0.00%	1			0.00%									
	%>10 µm			0.00%				0.00%									
	%>20 µm			0.00%				0.00%									
								EV72.10									
Spray Pattern	2.5 cm	ALB-006	Shape	passes	1			passes									
	5.0 cm		Shape	passes				passes									
			Size < 3 cm	passes				passes									
	7.5 cm		Shape	passes				passes									

Turn impinger? plume geometry?

Checked by

Table 2
Unit Spray Content
Albuterol Batch No. 92047

WAX
V01-8.1
ANDA 73-272

Beginning Shot No. 11-12

Can No.	W1 (g)	W2 (g)	Shot 11-12 (mcg)
1	28.282	28.108	98.3
2	28.306	28.128	79.8
3	28.264	28.098	77.9
4	28.235	28.062	75.4
5	28.321	28.151	91.0
6	28.295	28.120	93.4
7	28.275	28.102	90.9
8	28.257	28.081	77.3
9	28.279	28.101	86.2
10	28.259	28.087	81.6

$\bar{X} = 85.1$
SD = 7.9
%, CV = 9.27

Middle Shot No. 101-102

Can No.	W1 (g)	W2 (g)	Shot 101-102 (mcg)
1	20.492	20.316	87.4
2	20.651	20.473	91.5
3	20.704	20.529	79.8
4	20.528	20.353	80.9
5	20.563	20.387	104.3
6	20.389	20.211	99.9
7	20.924	20.753	99.6
8	20.596	20.420	91.0
9	21.005	20.827	88.9
10	20.820	20.644	85.1

$\bar{X} = 90.8$
SD = 8.23
%, CV = 9.06

End Shot No. 199-200

Can No.	W1 (g)	W2 (g)	Shot 199-200 (mcg)
1	12.494	12.318	83.7
2	12.837	12.660	87.9
3	12.642	12.468	83.8
4	12.344	12.170	76.0
5	12.057	11.876	108.8
6	11.890	11.720	97.5
7	12.566	12.390	109.8
8	12.488	12.311	102.7
9	12.676	12.499	94.4
10	12.759	12.583	86.3

$\bar{X} = 93.1$
SD = 11.4
%, CV = 12.3

W1: canister weight prior to discharge
W2: canister weight after discharge

Ventolin Batch No. Z3040205

IVAX
ANDA 73-27
Vol. 8.1
1

Beginning Shot No. 11-12

Can No.	W1 (g)	W2 (g)	Shot 11-12 (mcg)
1	27.730	27.556	82.7
2	27.764	27.591	82.0
3	27.855	27.685	74.5
4	27.645	27.472	92.2
5	27.699	27.526	89.1
6	27.508	27.331	86.8
7	27.683	27.499	89.0
8	27.563	27.390	82.2
9	27.594	27.414	88.7
10	27.656	27.485	85.8

$\bar{x}$ = 85.3
SD = 5.10
%CV = 5.97

Middle Shot No. 101-102

Can No.	W1 (g)	W2 (g)	Shot 101-102 (mcg)
1	20.370	20.201	66.2
2	20.266	20.093	88.8
3	20.550	20.382	79.7
4	20.050	19.881	91.2
5	20.050	19.841	83.5
6	19.873	19.702	92.5
7	20.278	20.106	81.4
8	20.318	20.146	85.3
9	20.086	19.903	88.3
10	20.281	20.110	85.8

$\bar{x}$ = 84.3
SD = 7.54
%CV = 8.95

End Shot No. 199-200

Can No.	W1 (g)	W2 (g)	Shot 199-200 (mcg)
1	12.426	12.256	93.9
2	12.139	11.966	87.5
3	12.618	12.452	87.1
4	11.955	11.785	90.8
5	12.982	11.809	94.6
6	11.678	11.509	97.5
7	12.228	12.054	90.3
8	12.471	12.299	91.2
9	11.946	11.769	91.0
10	12.412	12.243	98.2

$\bar{x}$ = 92.2
SD = 3.78
%CV = 4.10

W1: canister weight prior to discharge
W2: canister weight after discharge

MEDISOL
74-072

COMPARATIVE UNIT SPRAY POTENCY

SPRAY # 11 - 12 (Beginning)

Albuterol Inhaler
Study II

Basis:

A: Assay determinations based on two sprays per assay, as per the Bioequivalence Guidelines.

B: 100% Potency is 90 mcg of Albuterol per spray.

C: Upper and Lower control limits are 125% and 75% respectively.

D: Medisol (Lot# 801-0008); Ventolin (Lot# Z30292BS)

Purpose:

To demonstrate uniformity & similarity of potency delivered from mouthpieces of Ventolin & Medisol Albuterol Aerosol MDI's at beginning sprays of the product can.

Result:

The potency of Ventolin and Medisol products at beginning of sprays is in a very narrow window, controlled well within limits. Can to can variation is insignificant and potency values are comparable for the Medisol and Ventolin products.

Data:

TEST: LOT 801-0008

REF: LOT Z30292BS

CAN NUMBER	Percent Potency	
	MEDISOL mcg	VENTOLIN
1	91.92 82.73	103.63 93.27
2	87.76 78.98	98.40 88.56
3	94.30 84.87	106.13 95.52
4	88.44 79.60	106.52 95.87
5	96.24 86.62	104.13 93.72
6	82.57 74.31	99.31 89.38
7	94.17 84.75	100.60 90.54
8	96.82 87.14	100.06 90.05
9	94.46 85.01	101.19 91.07
10	88.93 80.04	98.82 88.94
$\bar{X}$	82.41	91.69
SD	4.07	2.70
%CV	4.94	2.95

11.2
10.8
11

MEDISOL NDA 74-072, VOL 2.1
11 JAN 95 - 3171

TABLE 17

MEDISOL
74-072

COMPARATIVE UNIT SPRAY POTENCY

SPRAY # 100 - 101 (Middle)

Albuterol Inhaler
Study II

Basis:

A: Assay determinations based on two sprays per assay, as per the Bioequivalence Guidelines.

B: 100% Potency is 90 mcg of Albuterol per spray.

C: Upper and Lower control limits are 125% and 75% respectively.

D: Medisol (Lot# 801-0008); Ventolin (Lot# Z30292BS)

Purpose:

To demonstrate uniformity & similarity of potency delivered from mouthpieces of Ventolin & Medisol Albuterol Aerosol MDI's at middle sprays of the product can.

Result:

The potency of Ventolin and Medisol products at middle of sprays is in a very narrow window, controlled well within limits. Can to can variation is insignificant and potency values are comparable for the Medisol and Ventolin products.

Data:

CAN NUMBER	Percent Potency	
	MEDISOL	VENTOLIN
1	93.18 (mg 83.86)	112.14 (mg 100.93)
2	98.94 (89.05)	102.42 (92.18)
3	93.40 (84.06)	106.19 (95.57)
4	99.29 (89.36)	110.33 (99.30)
5	94.44 (85.00)	92.70 (83.43)
6	87.78 (79.00)	102.38 (92.14)
7	99.71 (89.74)	104.23 (93.81)
8	105.66 (95.09)	98.44 (88.60)
9	105.08 (94.57)	100.97 (90.87)
10	106.42 (95.78)	103.29 (92.96)
$\bar{X}$	88.55	92.98
SD	5.57	5.02
%CV	6.29	5.40

TABLE 18

MEDISOL
74-072

COMPARATIVE UNIT SPRAY POTENCY

SPRAY # 199 - 200 (End)

Albuterol Inhaler
Study II

Basis:

A: Assay determinations based on two sprays per assay, as per the Bioequivalence Guidelines.

B: 100% Potency is 90 mcg of Albuterol per spray.

C: Upper and Lower control limits are 125% and 75% respectively.

D: Medisol (Lot# 801-0008); Ventolin (Lot# Z30292BS)

Purpose:

To demonstrate uniformity & similarity of potency delivered from mouthpieces of Ventolin & Medisol Albuterol Aerosol MDI's at <u>end</u> sprays of the product can.

Result:

The potency of Ventolin and Medisol products at <u>end</u> of sprays is in a very narrow window, controlled well within limits. Can to can variation is insignificant and potency values are comparable for the Medisol and Ventolin products.

Data:

CAN NUMBER	Percent Potency	
	MEDISOL mg	VENTOLIN mg
1	101.17 91.05	117.13 105.92
2	100.86 90.77	107.34 96.61
3	113.31 101.98	117.56 105.80
4	97.68 87.91	122.38 110.14
5	105.08 94.57	107.17 96.45
6	102.94 92.65	107.70 96.93
7	103.90 93.51	106.22 95.60
8	113.60 102.24	106.83 96.15
9	105.21 94.69	103.80 93.42
10	106.76 96.08	109.36 98.42
$\bar{X}$	94.55 mg	99.49
SD	4.62	5.55
%CV	4.89	5.57

TABLE 19

MEDISOL
74-072

COMPARATIVE UNIT SPRAY POTENCY

Average on 10 Cans

Albuterol Inhaler
Study II

Basis:

A: Assay determinations based on two sprays per assay, as per the Bioequivalence Guidelines.

B: 100% Potency is 90 mcg of Albuterol per spray.

C: Upper and Lower control limits are 125% and 75% respectively.

D: Average of potency values for begining, middle and end of can.

E: The begining, middle and end values were compared in separate charts preceeding this.

F: Medisol (Lot# 801-0008); Ventolin (Lot# Z30292BS)

Purpose:

To demonstrate uniformity & similarity of potency delivered from mouthpieces of Ventolin & Medisol Albuterol Aerosol MDI's throughout all spray stations of the product can.

Result:

The potency of Ventolin and Medisol products throughout all spray stations is in a very narrow window, controlled well within limits. Can to can variation is insignificant and potency values are comparable for the Medisol and Ventolin products.

Data:

CAN NO.	MEDISOL Percent Potency				VENTOLIN Percent Potency			
	BEGINING	MIDDLE	END	AVERAGE	BEGINING	MIDDLE	END	AVERAGE
1	91.92	93.18	101.17	95.42	103.63	112.14	117.13	110.97
2	87.76	98.94	100.86	95.85	98.40	102.42	107.34	102.72
3	94.30	93.40	113.31	100.34	106.13	106.19	117.56	109.96
4	88.44	99.29	97.68	95.14	106.52	110.33	122.38	113.08
5	96.24	94.44	105.08	98.59	104.13	92.70	107.17	101.33
6	82.57	87.78	102.94	91.10	99.31	102.38	107.70	103.13
7	94.17	99.71	103.90	99.26	100.60	104.23	106.22	103.68
8	96.82	105.66	113.60	105.36	100.06	98.44	106.83	101.78
9	94.46	105.08	105.21	101.58	101.19	100.97	103.80	101.99
10	88.93	106.42	106.76	100.70	98.82	103.29	109.36	103.82

TABLE 20

APR 29 1997

Albuterol Inhalation Aerosol
90 µg/actuation
ANDA **73-045**
Reviewer: Z.Z. Wahba
73045s3.695

A.L. Laboratories
Baltimore, MD
Submission Dates:
September 09, 1996
September 11, 1996

AMENDMENT TO A REVIEWED IN VIVO BIOEQUIVALENCE STUDY
(Continuation of the Review Dated Sept. 03, 1996)

BACKGROUND

The submission was reviewed and was found incomplete by the Division of Bioequivalence (review dated 9/03/96, ANDA #73-045) due to problems cited in the deficiency comments.

In this submission, the firm has responded to the deficiency comments and included additional information in the current submission.

Comment #1
The following items are needed for completion of the evaluation of the in vivo bioequivalence study. These items should be provided on paper copies (spread sheets) as well as on a floppy diskette (ASCII formate):

> Complete raw data for all FEV_1 measurements, during screening and subject inclusion phases for the 25 subjects used in the bioeqivalence study. This should include baseline FEV_1 measurements for each study day including subject screening and inclusion phase, as well as all FEV_1 measurements associated with each and every challenge dose. The number of breaths of methacholine associated with each and every challenge dose should also be reported.

Response to Comment #1
> The firm has provided the raw data that was requested in comment #1.
>
> The firm's response to comment #1 is acceptable.

Comment #1a
> Raw data on subject inclusion qualification criteria showing that there was a minimum eight-fold increase over baseline in response to two actuations of Ventolin® Inhalation Aerosol and a minimum two-fold ratio of response to two actuations relative to one actuation of Ventolin® Inhalation Aerosol. Include an example(s) of the method of calculation

that was used for subject inclusion qualification criteria.

Response to Comment #1a

The firm has provided the raw data that was requested in comment #1a. In addition to examples of the method of calculation.

The firm's response to comment #1a is acceptable.

Comment #1b

With regard to the data on the individual FEV_1 efforts for the bronchoprovocation study (Data submitted by the firm on June 19, 1995, in two tables, located in volume B9.1, p #05-#25).

i. For Table #1 (baseline FEV_1 data prior to morning and afternoon challenges for treatment phases only).

The data for subjects #113, 114, 115, 116, 119, 121, 122 (visits 1, 2 and 3) and 123 are not provided.

ii. For Table #2 (raw FEV_1 data for treatment phases only).

The data for subjects #113, 114, 115, 116, 119, 121, 122 (visits 1, 2 and 3) and 123 are not provided.

Response to Comment #1b

Subjects #113, 114, 115, 116, 119, 121, 122 (visits 1, 2 and 3) and 123 were tested on a Koko spirometer from which there is no paper tape printout, and only the highest FEV_1 of each set was recorded. The firm has provided the data that was requested in two Tables (see volume #B11.1, pages 9-10 and 37-64).

The firm's response to comment #1b is acceptable.

Comment #2

Please provide the equation that was used to estimate the Post-albuterol PD_{20} (cumulative mg). In addition, the firm should provide examples of its calculations for this value for a number of subjects. These examples should include subjects who had relatively high and relatively low post-albuterol PD_{20} values.

Response to Comment #2

The equation is

$$PD_{20} = \text{Dose 1} + \frac{(\text{Dose 2} - \text{Dose 1})(20 - \text{Response 1})}{(\text{Response 2} - \text{Response 1})}$$

Where:

Dose 1= second to last dose resulted in just less than a 20% decrease in FEV_1 compared to Saline FEV_1
Dose 2= last dose resulted in a $\geq$ 20% decrease in FEV_1 compared to Saline FEV_1
Response 1= % decrease in FEV_1 caused by Dose 1
Response 2= % decrease in FEV_1 caused by Dose 2

- The firm provided number of examples for its calculation (see, vol. #B11.1, pages 10-13 and 37-58).

The firm's response to comment #2 is acceptable.

Comment #3

In the validation report section (Vol. A8.1, page #116), the firm is requested to provide equations and its calculations for subject #1, both morning and afternoon visits.

Response to Comment #3

The requested information is provided in volume #B11.1, on pages 14, 59 and 60.

The firm's response to comment #3 is acceptable.

Comment #4

The raw data for the challenge studies should include the actual date of dosing of the treatment phase, gender and age, body weight, height, and predicted FEV_1 for age, gender and height, in addition to the data on baseline , saline control and FEV_1 at each challenge dose.

Response to Comment #4

The requested information is provided in volume #B11.1, on pages 61-64.

The firm's response to comment #4 is acceptable.

Statistical Analysis and Comparative In Vivo Performance:

The statistical analysis to determine bioequivalence of the test and reference products was based on the `response scale'. Analyses of the data were performed by the Division of Biometrics, HFD-700.

The following statistical approaches were applied:
1. Conventional analyses.
2. Scaling of the bioequivalence interval based on the intra-subject variability of the reference product.

The evaluation analyses are described below:

1. **Conventional analyses:**

The conventional analyses were performed without and with using the pre-albuterol PD_{20} as covariate. These analyses were carried out for log-transformed (Ln) post-albuterol PD_{20} and Drug Activity Ratio (DAR). Analyses were carried out using SAS PROC MIXED.

a. Response Scale-Conventional Analyses without use of Pre-albuterol PD_{20} as Covariate

In these analyses, three models were considered: (1) a model that assumed no period effect, (2) a model that assumed that period effects might be present and (3) a model with period effects and the linear trend of the study day. The results of these analyses are summarized below in terms of point estimates and 90% confidence intervals for the ratio of test product average response over reference product average response.

Table 1. Response Scale-Conventional Analyses without use of Pre-albuterol PD_{20} as Covariate

Model	Ln(Post-Albuterol PD_{20})		Ln (DAR)	
	Point Estimate	90% CI	Point Estimate	90% CI
No Per. Eff.	80.24%	67.18, 95.83	89.35%	73.66, 108.37
With Per. Eff.	80.45%	67.40, 96.04	89.53%	73.53, 109.00
With Per. & Day	80.38%	67.36, 95.92	89.36%	73.32, 108.92

Comments:

i. Results of conventional analyses (no per., with per., and with per. & day) showed that the 90% confidence intervals for the log-transformed PD_{20} fall within the range of 67-150% previously considered by OGD for the approval of generic albuterol MDI's.

ii. Drug Activity Ratios (DAR) were calculated as secondary data analyses recommended in the OGD interim guidance. The DAR analysis is intended to assist an evaluation of adjustment of postdose PD_{20} for the baseline PD_{20} obtained on the same day. In addition, it serves as a

potential future reference in the development of a bioequivalence standard for albuterol inhalation aerosols.

iii. Note: The 1994 OGD interim guidance states that the primary data analysis of given bioequivalence data should be based on postdose PD_{20}.

b. Response Scale-Conventional Analyses with use of Pre-albuterol PD_{20} as Covariate

Several analyses were carried out in which Log pre-albuterol PD_{20} (LPRE) was used as a covariate. The summary of the analyses are the following:

i. All confidence intervals using LPRE as a covariate, regardless of the statistical model used, fell within the limits of 67% to 150%.

ii. The 90% confidence limits depended on which factors were included in the statistical model. One model had shown a lower limit of the 90% confidence interval ranged from 69.82% to 73.91%, and the upper limit of the 90% confidence interval ranged from 99.67% to 106.18%. For the overwhelming majority of the models considered, the lower 90% confidence limit was greater than 70%.

iii. These results (Analyses with use of Pre-albuterol PD_{20} as Covariate) appear to support the conclusion from the analyses without covariate, that the study data has established that the average response to the A. L. Labs product, divided by the average response to the reference product, Ventolin®, lies within the limits of 67% to 150%, for both LPOST and LDAR.

2. Scaling Of Bioequivalence Limits to the Reference Product Within-Subject Standard Deviation:

Two analyses were carried out for this scaling approach. The purpose of the two analyses was to assess whether bioequivalence had been demonstrated if the bioequivalence limits are scaled to the reference product within-subject standard deviation. These analyses used bootstrap methodology [specifically, the Bias-Corrected and Accelerated (BCa) method as described in the 1993 textbook of Efron and Tibshirani, 100,000 bootstrap samples per run] to obtain 90% confidence intervals for the quantity,

$$[Ln(muT) - Ln(muR)]/\sigma_{WR}$$

where: muT is the population geometric mean response for the Test product, muR is the population geometric mean response for the reference product, and σ_{WR} is the reference product within-subject standard deviation on the log scale. In the first analysis, it was assumed that there were no period effects in the study (Without Period Effect). In the second analysis, the analysis allowed for period effects (With Period Effect).

Table 2. The 90% bootstrap confidence limits

Model	Metric	90% bootstrap confidence Limits (Ln-Units)
Without Period Effect	Post-albuterol PD_{20}	-0.7221, -0.0889
	DAR	-0.5284, 0.1282
With Period Effect	Post-albuterol PD_{20}	-0.7916, -0.0744
	DAR	-0.5644, 0.1694

The bioequivalence limits to which these confidence intervals are compared are plus-or-minus $(\ln 1.25)/\sigma_{W0}$.
For the choices of σ_{W0}= 0.30, 0.25 and 0.20, these limits are as follows:

Table 3. Bioequivalence Limits

σ_{W0}	$(\ln 1.25)/\sigma_{W0}$	Bioequivalence Limits (Ln-units)
0.30	0.7438	-0.7438, 0.7438
0.25	0.8926	-0.8926, 0.8926
0.20	1.1157	-1.1157, 1.1157

Comments:

i. The scaling of bioequivalence limits become less stringent as the value of σ_{W0} is decreased, and more stringent as the value of σ_{W0} is increased.

ii. Using the analyses with no period in the model, the study would pass for LPOST for σ_{W0} =0.309 or lower, and would pass for LDAR for σ_{W0} =0.422 or lower.

iii. Using the analyses with period in the model, the study would pass for LPOST for σ_{W0} =0.282 or lower, and would pass for LDAR for σ_{W0} =0.395 or lower.

OVERALL COMMENTS:

1. The statistical analysis to determine bioequivalence of the test and reference products was based on the `response scale'. Analyses of the data were performed by the Division of Biometrics, HFD-700.

2. Results of conventional analyses with or without period effect showed that the 90% confidence intervals for the log-transformed PD_{20} fall within the range of 67-150% previously considered by OGD for the approval of generic albuterol MDI's.

   Note: The 1994 OGD interim guidance states that the primary data analysis of given bioequivalence data should be based on postdose PD_{20}.

3. Drug Activity Ratios (DAR) were calculated as secondary data analyses recommended in the OGD interim guidance. The 90% confidence intervals for the log-transformed DAR fall within the range of 67-150%. The DAR analysis is intended to assist an evaluation of adjustment of postdose PD_{20} for the baseline PD_{20} obtained on the same day. In addition, it serves as a potential future reference in the development of a bioequivalence standard for albuterol inhalation aerosols.

4. An alternative analysis, based on scaling the bioequivalence limits to the reference product's within-subject standard deviation, was conducted. The 90% confidence interval limits for the pivotal post-dose PD_{20} data pass the test for σ_{W0} = 0.282 or lower.

RECOMMENDATION:

1. The in vivo bioequivalence study conducted by A.L. Laboratories on its drug product, albuterol inhalation aerosol, 90 µg per actuation, lot #6403, comparing it to Ventolin® manufactured by Allen & Hanburys (a Division of Glaxo), has been found acceptable by the Division of Bioequivalence. Thus, A.L. Laboratories' albuterol inhalation aerosol, 90 µg per actuation is bioequivalent to the reference drug product, Ventolin® (Allen & Hanburys, a Division of Glaxo).

2. The firm has not yet conducted acceptable in vitro testing on the test product. Thus, the application is still incomplete.

Zakaria Z. Wahba, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALED RMHATRE
FT INITIALED RMHATRE 2/27/97

Concur: _____ Date: 4/29/97
Rabindra Patnaik, Ph.D.
for ~~Acting~~ Director
Division of Bioequivalence

cc: ANDA 73-045 (original, duplicate), HFD-600 (Hare), HFD-630, HFD-658 (Mhatre, Wahba), Drug File, Division File

ZZWahba/030796/032596/061096/070596/071596/082596/082996/092396/101596/file #73045s3.695

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

ANDA 73-045

MAY 12 1997

A.L.Laboratories, Inc.
Attention: Deborah Winkel
The Johns Hopkins Research Campus
333 Cassell1 Drive, Suite 3500
Baltimore, MD 21224

Dear Madam:

Reference is made to your Abbreviated New Drug Application, and the amendments submitted on September 9, 11 and 20, October 8 and November 15, 1996 and January 6 and 22, 1997 for Albuterol Inhalation Aerosol (MDI), 90 ug/actuation.

Reference is also made to the telephone conference of February 28, 1997 between Ron Bynum, and Wallace Adams, Gur Jai Pal Singh and Lizzie Sanchez of the Office of Generic Drugs; and to the FAX request for information issued on March 5, 1997 as a follow-up to that telephone conference. The Division has not received any new data in response to our request.

The Office of Generic Drugs has reviewed the bioequivalence data previously submitted and the same comments provided in the above communications are forwarded:

1. Because drug delivery may change progressively through canister life, the Division of Bioequivalence believes that, as a bioequivalence criterion, a test product should meet USP <905> Content Uniformity requirements at beginning, middle and end of canister through-life. Therefore, please provide the following:

   a. Content uniformity data on 30 canisters of test lot # 8457 at beginning, middle and end.

   b. Content uniformity data on 10 canisters of test lots # 8671 and 8834 at beginning, middle and end. For each batch, if 10 canisters fail to meet the USP specification at each of beginning, middle and end, an additional 20 canisters should be tested as stated in USP <905>. Note that, consistent with the 27 June 1989 Division of Bioequivalence *Guidance for the In Vitro Portion of Bioequivalence Requirements for Metaproterenol Sulfate and Albuterol Inhalation Aerosols (Metered Dose Inhalers)*, the specifications will be evaluated separately at beginning, middle and end of canister through life.

   c. Data may be provided in the same format as that on pages 430 and 431 of the 6 January 1997 submission.

2. Additional information is also requested by the Division of Bioequivalence:

   a. The specific model of cascade impactor used by the firm for the data submitted on 6 January 1997.

   b. The expiration dates for test product batches # 8671 and 8834.

   c. Testing dates for the twin impinger data submitted on 12 June 1995 and 27 July 1996.

   d. Conduct of the Microscopy Test (USP <601>) on canisters from test product batches # 8457, 8671, and 8834, and Ventolin MDI batch # 6ZP0756. The Division requests these comparative baseline data, noting that the test serves a number of purposes: determination of the number of particles larger than 10 microns; identification of unusual agglomeration; characterization of crystal morphology; and identification of foreign particulates not related to the drug substance.

As described under 21 CFR 314.96 an action which will amend this application is required. The amendment will be required to address all of the comments presented in this letter. Should you have any questions, please call Lizzie Sanchez, Pharm.D., Project Manager, at (301) 827-5847. In future correspondence regarding this issue, please include a copy of this letter.

Sincerely yours,

Nicholas Fleischer, Ph.D.
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

APR 29 1997

Albuterol Inhalation Aerosol (MDI)
90 µg/actuation
ANDA 73-045
Reviewer: Gur J.P. Singh
73045def.197

A.L. Laboratories
Submission Date:
~~Sept. 20~~ and Nov. 15, 1996,
Jan. 6 and 22, 1997

Review of Correspondence Related to In Vitro *Bioequivalence Study Data*

The Division of Bioequivalence (DBE) *Guidance for the In Vitro Portion of Bioequivalence Requirements for Metaproterenol Sulfate and Albuterol Inhalation Aerosols (Metered Dose Inhalers)*, issued June 27, 1989, recommends comparative data to characterize *in vitro* performance of the test product relative to that of the reference listed drug.

The firm's June 12, 1995, submission provided comparative data for the test and the reference product. A DBE review of the firm's *in vivo* and *in vitro* data, dated July 17, 1996, included a list of deficiencies which were communicated to the firm in a July 18, 1996 letter. The firm's August 1,1996, amendment responded to those deficiencies.

Data submitted up to August 1, 1996 were reviewed by the Division of Bioequivalence. Based on the September 3, 1996 review, the Division of Bioequivalence issued a letter to the firm (Letter Date: September 3, 1996). With regard to the *in vitro* performance data this letter listed a variety of deficiencies. On September 20 and November 15, 1996, the sponsor submitted its responses to these deficiencies. These submissions were reviewed and the application was still found to be incomplete. On November 21, 1996, the sponsor was informed of a variety of deficiencies, and it was requested to repeat some of the *in vitro* tests on lots of test and reference products within their expiry date. The sponsor submitted response to these deficiencies on January 6 and 22, 1997.

Data submitted up to January 22, 1997 were reviewed, and application was still found to be incomplete due to the deficiencies given below. The sponsor was informed of these deficiencies in a tele-conference on February 28, 1997, and via fax on March 5, 1997 (attachments).

Deficiencies:

1. Because drug delivery may change progressively through canister life, the Division of Bioequivalence believes that, as a bioequivalence criterion, a test product should meet USP <905> Content Uniformity requirements at beginning, middle and end of canister through-life. Therefore, the firm is requested to provide the following:

a. Content uniformity data on 30 canisters of test lot # 8457 at beginning, middle and end.

b. Content uniformity data on 10 canisters of test lots # 8671 and 8834 at beginning, middle and end. For each batch, if 10 canisters fail to meet the USP specification at each of beginning, middle and end, an additional 20 canisters should be tested as stated in USP <905>. Note that, consistent with the 27 June 1989 Division of Bioequivalence *Guidance for the In Vitro Portion of Bioequivalence Requirements for Metaproterenol Sulfate and Albuterol Inhalation Aerosols (Metered Dose Inhalers)*, the specifications will be evaluated separately at beginning, middle and end of canister through life.

c. Data may be provided in the same format as that on pages 430 and 431 of the 6 January 1997 submission.

2. Additional information is also requested by the Division of Bioequivalence:

a. The specific model of cascade impactor used by the firm for the data submitted on 6 January 1997.

b. The expiration dates for test product batches # 8671 and 8834.

c. Testing dates for the twin impinger data submitted on 12 June 1995 and 27 July 1996.

d. Conduct of the Microscopy Test (USP <601>) on canisters from test product batches # 8457, 8671, and 8834, and Ventolin MDI batch # 6ZP0756. The Division requests these comparative baseline data, noting that the test serves a number of purposes: determination of the number of particles larger than 10 microns; identification of unusual agglomeration; characterization of crystal morphology; and identification of foreign particulates not related to the drug substance.

Recommendation

1. The in vitro performance data submitted by A.L. Laboratories on its albuterol metered dose inhaler has been found to be incomplete due to deficiencies #1 and 2. The sponsor was informed of these deficiencies previously. Further review of this application will not be conducted till the sponsor submits satisfactory response to deficiencies #1 and 2 .

Gur Jai Pal Singh, Ph.D.
Division of Bioequivalence
Review Branch II

RD INITIALED SNERURKAR
FT INITIALED SNERURKAR 4/29/1997

CONCUR: _____ DATE 4/29/97
for Nicholas Fleischer, Ph.D.
Director
Division of Bioequivalence

GJP SINGH/ 4/29/97 73045def.197

CC: ANDA# 73-045 (Original, duplicate), HFD-600 (Hare), HFD-130 (Jallen), HFD-655 (Nerurkar, Singh), Drug file, Division file.

RECORD OF TELEPHONE CONVERSATION/MEETING

The following requests were provided for the firm:

1. Content uniformity data on 30 canisters of test lots #8671 and #8834 at beginning, middle and end. For each batch, if 10 canisters fail to meet the USP specifications at each of beginning, middle, and end, an additional 20 canisters should be tested as stated in USP <905>. Data may be provided in the same format as that on pages 430 and 431 of the January 6, 1997.

2. The specific model of cascade impactor used by the firm for the data submitted on Jan 6, 1997.

3. The expiration dates for the test product batches #8671 and #8834.

4. Testing dates for twin impinger data submitted on 12 June 95 and 27 July 1996.

5. Microscope test for 3 test batches and the batch from the reference product according to USP specifications.

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73045.003

DATE
2/28/97

ANDA NUMBER
73045

IND NUMBER

TELECON

INITIATED BY **MADE**
_ **APPLICANT/ SPONSOR** = **BY TELE.**
X **FDA** _ **IN PERSON**

PRODUCT NAME
Albuterol MDI

FIRM NAME
A.L. Pharma

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD
Ron Bynum
Dr. Schumaker

TELEPHONE NUMBER
(410) 558-7250
x 208

SIGNATURE
Wallace Adams
Gur Singh
L. Sanchez

3/5/97

Ron Bynum
A.L. Pharma
Albuterol MDI/ANDA 73-045

1. Because drug delivery may change progressively through canister life, the Division of Bioequivalence believes that, as a bioequivalence criterion, a test product should meet USP <905> Content Uniformity requirements at beginning, middle and end of canister through-life. Therefore, the firm is requested to provide the following:

    a. Content uniformity data on 30 canisters of test lot # 8457 at beginning, middle and end.

    b. Content uniformity data on 10 canisters of test lots # 8671 and 8834 at beginning, middle and end. For each batch, if 10 canisters fail to meet the USP specification at each of beginning, middle and end, an additional 20 canisters should be tested as stated in USP <905>. Note that, consistent with the 27 June 1989 Division of Bioequivalence *Guidance for the In Vitro Portion of Bioequivalence Requirements for Metaproterenol Sulfate and Albuterol Inhalation Aerosols (Metered Dose Inhalers)*, the specifications will be evaluated separately at beginning, middle and end of canister through life.

    c. Data may be provided in the same format as that on pages 430 and 431 of the 6 January 1997 submission.

2. Additional information is also requested by the Division of Bioequivalence:

    a. The specific model of cascade impactor used by the firm for the data submitted on 6 January 1997.

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    d. Conduct of the Microscopy Test (USP <601>) on canisters from test product batches # 8457, 8671, and 8834, and Ventolin MDI batch # 6ZP0756. The Division requests these comparative baseline data, noting that the test serves a number of purposes: determination of the number of particles larger than 10 microns; identification of unusual agglomeration; characterization of crystal morphology; and identification of foreign particulates not related to the drug substance.

JUL 14 1997 DIV

Albuterol Inhalation Aerosol (MDI)
90 µg/actuation
ANDA 73-045
Reviewer: Gur J.P. Singh
73045I.O97

ALPHARMA
(A.L. Laboratories)
Submission Date:
May 23, 1997.

Review of Correspondence Related to In Vitro *Bioequivalence Study Data*

The Division of Bioequivalence *Guidance for the In Vitro Portion of Bioequivalence Requirements for Metaproterenol Sulfate and Albuterol Inhalation Aerosols (Metered Dose Inhalers)*, issued June 27, 1989, recommends comparative data to characterize *in vitro* performance of the test product relative to that of the reference listed drug (RLD). This guidance (hereafter referred to as the 1989 Guidance) did not set specifications for the requested tests. There is no USP monograph for Albuterol Inhalation Aerosol. However, the data will be compared with the specifications set in USP Chapters 601 and 905, where applicable.

The firm's June 12, 1995, submission provided comparative data. A DBE review of the firm's *in vivo* and *in vitro* data, dated July 17, 1996, included a list of deficiencies of the *in vitro* data, which were communicated to the firm in a July 18, 1996, letter. The firm's August 1,1996, amendment responded to those deficiencies.

Data submitted up to August 1, 1996, were reviewed by the Division of Bioequivalence. Based on the September 3, 1996 review, the Division of Bioequivalence issued a letter to the firm (Letter Date: September 3, 1996) which listed a variety of deficiencies. On September 9 and 11, 1996, the sponsor submitted its responses to these deficiencies. That submission was reviewed and the application was still found to be incomplete. On November 21, 1996, the sponsor was informed of a variety of deficiencies, and it was requested to repeat some of the *in vitro* tests on lots of test and reference products that were still within their expiry dates. The sponsor submitted its response in January 6 and 22, 1997, amendments. These data were reviewed and the application was still found to be incomplete due to a variety of deficiencies. A list of these deficiencies was conveyed to the firm in a tele-conference on February 28,, 1997, and a Division of Bioequivalence letter on May 12, 1997. The sponsor has now submitted another amendment dated May 23, 1997.

This review is based principally on the data submitted on January 6, and 22, and May 23, 1997. Reference is made to previous data, where necessary/applicable.

The MDI's used for *in vitro* testing were from the following batches:

Ventolin^{R} Inhalation Aerosol 90 µg/actuation (The reference Product), manufactured by Allen & Hanburys, Division of Glaxo, Lot #6ZP0756. Expiry Date: April, 1999

Albuterol Inhalation Aerosol 90 µg/actuation (Test Product), manufactured for A.L. Laboratories by Production Lot #8457 Expiry date: December, 1997.

For some tests the sponsor has also submitted data for two additional production batches of the test product (lot #8671- expiry date February 1998, and lot 8834, expiry date April 1998).

Documentation of bioequivalence requires the use of tests based on validated methods. For the tests used for potency estimation and particle size distribution cascade imopactor) the sponsor has used a validated . Albuterol concentrations in various samples were determined by

Required details and data for method validation are given in the January 6, 1997, amendment, a summary of these data are given below:

Accuracy (% of nominal concentrations):

Cascade impaction: 90.7% - 109.6% (in the range of 0.09 - 6 μg/mL)

Potency estimation: 97.7% - 103.8% (in the range of 1 - 3 μg/mL)

Precision (%CV): 7.9% - 13.3%

Limit of quantitation: 0.07 μg/mL with a %CV of 7.1-10.1.

Limit of detection: 0.03 μg/mL with signal:noise ratio of 4:1.

Linearity: Linearity was demonstrated for calibration curves based or ı the range of 0.07 μg/mL - 6 μg/mL, based on correlation coefficients of 0.99 or above.

Stability: Data submitted by the sponsor supports stability of samples at room temperature up to 11 days.

The sponsor has used a variety of procedures. Among these procedures, methods used for determination of Unit Spray Sampling and Potency Estimation have been tested by the FDA laboratory in St. Louis. These methods have been found to be satisfactory, based on reviewer's communication with the Division of Chemistry (OGD).

I. **Content Uniformity (Unit Spray Content Test)**

Estimation of unit dose performed by the firm is equivalent to the potency estimation described in the 1989 Guidance. It is also referred to as unit spray content in USP 23, chapters 601. The flow rate used in this test was 12.5 L/min recommended in the USP as the most satisfactory flow rate (USP, pp 1762). The sponsor has set a specification for unit dose in the range of 75.0% to 125.0% of the label claim . The USP specifications for the uniformity of dosage units are as follows:

> Not more than 1 of the 10 dosage units lies outside the range of 75-125% (67.5 - 112.5 μg) of the label claim and no unit lies outside the 65-135% (58.5 - 121.5 μg) of the label claim.
>
> If the above requirement is not met, test another 20 units. The Content Uniformity is met if no more than 3 (out of 30) units are outside the range of 75-125% of the label claim and no unit lies outside the 65-135% of the label claim.

Determination of albuterol per actuation was based on a chemical assay. In this test, a primed unit was actuated into a collection tube attached to a gas chamber (similar to the USP sampling apparatus/single stage impactor), with a flow of air generated by a vacuum line. The drug was collected in a mixture of water and methanol and assayed Based on the January 6 submission (pp 430, vol 13.1), the results are as follows:

Testing Stage	Unit Dose (μg)				Test/Ref (p)
	Test (8457)		Reference		
	Mean	Range	Mean	Range	
Beg. (11-12)	86.1 (10.4)		78.8 (5.4)		1.09 (<0.05)
Mid. (100-101)	75.7 (12.8)		82.5 (3.4)		0.91 (<0.05)
End (199-200)	86.7 (13.3)		87.3 (4.6)		0.99 (>0.05)
Overall	82.8 (13.3)		82.9 (6.1)		0.99 (>0.05)

The *Unit Dose data are given as mean (%CV) of 10 experiments.*

**Out of ten units, three were outside sponsor's specifications of 67.5 -112.5 μg/spray when tested at the middle of the canister life..*

Observations:

- The ranges of unit dose of the test product meet sponsor's specifications at the Beginning and End stages of the MDI life. However *3 of the 10 units at the middle* of the canister life were outside the 75-125% of the label claim, no unit was outside the 65-135% of the label claim.

- On an average the unit dose delivered by the test products was within 10% of that delivered by the reference product. The inter-unit variability for the test product was greater than that of the reference product, as indicated by %CV's given in parentheses.

Because, based on the data submitted by the sponsor on January 6, 1997, the test product did not meet USP test of content uniformity of dosage forms, the sponsor was requested to test content uniformity of additional 30 units of lot #8457, and 10 units of lot #8671 and #8834. These data were submitted on May 23, 1997 (vol 14.1). The results of this testing are summarized as follows:

Testing Stage	Unit Dose (μg)		
	Lot 8457 (n=30)	Lot 8671 (n=10)	Lot 8834 (n=10)
Beg (11-12)	87.2 (13.9),	82.1 (4.9)	91.7 (9.0),
Mid(100-101)	83.9 (13.6)	77.7 (8.2)	91.2 (9.0)
End(199-200)	86.1 (15.1)	76.5 (5.7)	91.5 (8.8)

The *Unit Dose data are given as mean (%CV), range.*
[a] *two of the 30 units are out of the 75-125% (67.5 -112.5 μg) of the label claim, but all units are within 65-135% (58.5 - 121.5 μg) of the label claim.*
[b] *three of the 30 units are out of the 75-125% (67.5 -112.5 μg) of the label claim, but all units are within 65-135%(58.5 - 121.5 μg) of the label claim.*
[c] *one of the 10 units is out of the 75-125% (67.5 -112.5 μg) of the label claim, but all units are within 65-135% (58.5 - 121.5 μg) of the label claim.*

Observations:

- Based on the results submitted on May 23, 1997, each of the three production lots of the test product meets the USP test of content uniformity at Beginning, Middle and End stages of testing.

- The May 23 amendment contains data for 30 units of lot 8457 in addition to the 10 units tested previously (January 6, 1997 amendment). USP specifications given in USP chapter <905> require a two-step testing, where 10 canisters are tested in the first step and another 20 tested in the second step. If the above data are evaluated in the manner described in the USP, only first 20 of the 30 units' data submitted on May 23 can be considered. If a total of 30 units are considered to be 10 units submitted on January 6 plus 20 units submitted on May 23, then:

  Two of the 30 units are out of the 75-125% of the label claim, but all units are within 65-135% of the label claim, at the Beginning stage.

  Three of the 30 units are out of the 75-125% of the label claim, but all units are within 65-135% of the label claim, at the Middle stage.

  Three of the 30 units are out of the 75-125% of the label claim, but all units are within 65-135% of the label claim, at the End stage.

The test product meets the USP test of content uniformity at the Beginning, Middle and End stages of testing.

II. Shot weight

Measurements of mean shot weights for two actuations at beginning, middle and end of each canister was performed. This test was performed in a manner similar to the test of the metering performance given in the USP (pp 1762), and its procedure was consistent with the 1989 Guidance. The raw data for all testing to determine shot weights are given on pages 430-31 of the January 6, 1997 supplement. Sponsor's specifications for the shot weight are: Overall mean - mg/spray, and individual determinations to be in the range of mg/spray. The results of shot weight measurements are summarized as follows:

Testing Stage	Shot Weight (mg)				Test/Ref (*p*)
	Test		Reference		
	Mean	Range	Mean	Range	
Beg. (11-12)	90.0 (2.0)		85.2 (1.9)		1.03 (<0.05)
Mid. (100-101)	86.9 (1.1)		83.8 (2.2)		1.04 (<0.05)
End (199-200)	86.9 (1.5)		84.1 (2.1)		1.03 (<0.05)
Overall	87.8 (2.1)		84.4 (2.1)		1.04 (<0.05)

The shot weight data are given as mean (%CV) of 10 experiments.

Observation:

Based on the shot weight data, test product's performance is comparable to that of the reference product; differences between the test and reference products are less than 5%. However, it is noteworthy that based on the unit spray content, differences between test and reference products are larger than the difference in shot weights of these products. In reviewer's opinion it may be partly due to differences between the two products in the amount of inactive ingredients delivered per actuation, and partly due to the sensitivity of methods of assessment (i.e., chemical assay versus gravimetric determination).

Shot weight data were also submitted on May 23 for 30 units of lot 8457 and 10 units from each of batches 8671 and 8834 (vol 14.1) All readings are within the above specifications set forth by the sponsor.

III. **Spray Pattern** : The January 6 and May 23, 1997, amendments do not contain new information on spray pattern. Spray pattern testing was performed using the lot #6403 of the test product and lot Z31383LS of the reference products. These batches expired in March 1996. Therefore data submitted on August 1, 1996 is not acceptable for product approval and the review is based on data submitted on June 12, 1995.

The spray pattern was determined on one spray per each of three canisters of test and RLD at each of three distances. Each can was placed in actuator and positioned, 2.5, 5.0 and 7.5 cm away and parallel to a 20 cm X 20 cm silica gel TLC spray. Single spray was fired (the canister was shaken before each spray) for each measurement. The resulting spots were viewed under UV light and the spray pattern was outlined

with a pencil. Longest and shortest diameters of the spot were measured and the mean diameter was calculated.

Results of spray pattern testing are summarized on page 127 of vol 10.1. Based on these data. the spray patterns of the test and reference product were comparable. In the absence of any compendial or Agency criteria. these data are acceptable.

IV. Particle Size

The 1989 Guidance requests particle size determination by two methods, with the cascade impactor data considered as pivotal. The sponsor used the multistage cascade impactor . laser diffraction, and microscopy to determine particle size distribution.

Andersen Cascade Impactor:

The cascade impactor apparatus 1 (USP 23, Chapter 601) is used to determine the mass median aerodynamic diameter (MMAD) and geometric standard deviation (GSD). The sponsor used ar cascade impactor with a terminal filter operated, at an airflow rate of 28.3 ± 0.3 L/min. The atomizing chamber used by the sponsor was similar to the one recommended by the USP. Data submitted on January 6, 1997 are based on experiments that used 15 actuations for each run. This number of actuations is consistent with the recommendation made in the 1989 guidance. No new data were submitted on May 23, 1997.

In this test, a primed unit was actuated into the atomizing chamber connected to the mpactor. The drug deposited on the oral adapter, valve stem, throat, and collection plates was washed off with methanol and assayed The final filter was also extracted with methanol.

IV A: DRUG DEPOSITION PROFILES: The amount of drug deposited on various stages of the cascade impactor was determined. Data showing amount of albuterol deposited at various stages based on the test and reference product's testing are presented in table 1 (attachment). In addition, table 2 show similar data for the three lots of the test product at beginning of the canister life (actuations 11-25). The reviewer has calculated the average amount of drug deposited at various stages, and the profiles of the average amount of drug deposited at each stage are shown in Figure 1 (attachment). These profiles show different deposition of albuterol at stage 5 of the cascade impactor. A comparison analysis (t-test) indicated statistically significant difference between the test and the reference product at this stage.

The reviewer also computed deposition profiles of the three lots of the test product used in this study. The results of these analyses presented in figure 2 (attachment) demonstrate comparable deposition profiles of the three lots of the test product at the beginning of the canister life (actuations 11-25).

IV B. MASS BALANCE: Material balance calculations were performed per USP method. The results of these calculations are summarized below:

Testing Stage	Material Balance (%)	
	Test (lot #8457)	Reference
Beg. (11-25) Mid.(76-90) End (186-200)		
Beg. (11-25)		Test lot #(8671)
Beg. (11-25)		Test lot #(8834)

Data are tabulated as range for three canisters .

IV C. MMAD and GSD Data

The USP or the 1989 Guidance do not provide specifications for MMAD and GSD.

SPONSOR SPECIFICATIONS:

MMAD: microns
GSD: Specifications not given
Respirable Fraction: Specifications not given

The results of the cascade impactor analysis for MMAD and GSD are given in tables 3 (attachment). The data are based on calculations performed by the reviewer and the sponsor. The reviewer used the computer program written by James Allgire and Moheb Nasr of the FDA St. Louis laboratory. This method uses data for albuterol deposition on stages 1 to 5.

Calculation of MMAD and GSD involves the use of Effective Cutoff Diameter (ECD) values. ECD values used by the sponsor were different from those employed by the FDA laboratory (see below).

Impactor Stage	ECD (microns) values used by	
	Sponsor	FDA Lab.
0	>8.6	9.0
1	8.6	5.8
2	5.9	4.7
3	4.7	3.3
4	3.3	2.1
5	1.8	1.10
6	0.85	0.65
7	0.53	0.43
Filter	0.29	Not given.

Another factor that influences the magnitude of MMAD and GSD values is number of stages included in calculation of these parameters. The sponsor has not mentioned the number of stages used for its analysis. The FDA laboratory's computer program uses data for stages 2-5 for computation of MMAD and GSD. The reviewer has calculated all MMAD and GSD values using that computer program. Separate calculations were done based on ECD values used by the sponsor and the FDA laboratory. The results of these analyses are summarized in table 3 and 4 (attachment).

Observations:

- The sponsor used 15 actuations of the MDI. as recommended in the guidance.
- The MMAD and GSD values (individual as well as mean) calculated by the reviewer are different from those reported by the sponsor, and these differences may be due to the method used for calculations. Furthermore, there was notable difference in the values of MMAD and GSD calculated based on the two ECD's (see table 3 and 4). These differences should not affect the test and reference product comparisons.
- Based on ECD values employed by the firm, MMAD values of the test product were 10-12% greater, and its GSD values were similar to the respective values for the reference product. Variation (%CV) was also comparable for these products. In these comparisons, differences in MMAD between the test and reference products were statistically significant (p <0.05).

- Based on ECD values employed by the FDA laboratory, MMAD values of the test product were 11-15% greater, and its GSD values were similar to the respective values for the reference product. Variation (%CV) was also comparable for these products. In these comparisons also, differences between the test and reference products were statistically significant ($p < 0.05$).

- Based on the mean or the overall mean values using sponsor's ECD's , the differences between the test and reference products MMAD were $\leq 0.43\ \mu$, and based on reviewer's calculations using FDA Laboratory's ECD's these difference were $\leq 0.33\ \mu$. These differences are also statistically significant. . Nonetheless there is no information available to OGD which indicates that MMAD difference of $< 0.5\mu$ may significantly affect bioavailability of albuterol delivered via an MDI.

- Differences between MMAD values for three production lots of the test product were not statistically significant. These data are indicative of consistency between these lots of the test product.

IV D. Respirable Dose (RD) and Respirable Fraction (RF) Data

$Beta_2$ receptors are located in smooth muscle from large and small airways. Receptors are found in the bronchi, the bronchioles, the airway epithelial cells, and in bronchial submucosal glands from the large bronchi to the terminal bronchioles. They are also found in the alveoli walls, although the pharmacologic significance of this is not known [Carstairs *et al., Am. Rev. Respir. Dis.*, 132: 541(1985)]. The "respirable dose" is frequently taken to be that drug less than 5.8 microns in diameter (see for example, Vidgren et al., *Pharm. Res.*, 11:1320(1994). Zanen et al., *Intern. J. Pharmac.*, 107: 211(1994), in a study of albuterol delivered as a monodisperse aerosol (NOT from an MDI), found that in mild asthmatics receiving cumulative doses of drug, a 2.8 micron aerosol (GSD < 1.2) induced a significantly better bronchodilation than did a 5 micron monodisperse aerosol. In view of the above information, to provide further insight into the cascade impactor data, the reviewer computed "respirable doses" and "respirable fractions" based on three different diameters - drug less than 5.8, 4.7 and 3.3 microns. Thus, for the 5.8 micron data, the amount of drug deposited on stages 2 - 7 and the filter (i.e., the amount of drug less than 5.8 microns) was computed. Similarly for the 4.7 micron data, the amount of drug deposited on stages 3 - 7 and the filter, and for the 3.3 micron data, the amount of drug deposited on stages 4 - 7 and the filter. The "respirable fraction" was computed as the "respirable dose" divided by the drug "ex-actuator" (i.e, the sum of drug deposited on the throat, and stages 0 - 7 of the cascade impactor and the terminal filter). The results of these calculations are given in tables 5 and 6 (attachment)

Observations:

- For drug less than 5.8, 4.7 and 3.3 microns, there were differences between the test and reference products in both the RD and RF, and for most RD's these differences were statistically significant. In the absence of compendial criteria for RD and RF, and the acceptable *in vivo* bioequivalence and safety of the test product, these data are acceptable.

- Differences between RD and RF values for three production lots of the test product were not statistically significant. These data are indicative of consistency between these lots of the test product.

IV E. Microscopy: In response to the agency requests of February 28 and May 23, 1997, the sponsor has performed the USP microscopy particle size test on test product batches 8457, 8671 and 8834 and Ventolin^{R} lot 6ZP0756. The USP test requires estimation of particle of ≥ 10 microns. Data submitted by the firm on microscopical examination of test and reference products are given in volume 14.1. Based on these data particle size distribution of the test product is comparable to that of the reference product.

IV F. Particle Sizing Using Laser: The sponsor has also determined the particle size distribution using droplet and particle size analyzer. This test was performed using the lot 6403 of the test product and lot Z31383LS of the reference product, and it was accomplished within the expiry dates of these batches (vol 8.2). The January 6 and May 23, 1997, amendments do not contain new data on this test.

In this experiment each canister was

. apparatus. The temperature of the down pipe was set at The sponsor has not provided specifications for this test. The laser diffraction data submitted by the firm (Volume 8.2) are summarized as follows:

	Particle size (μM)		Test/Ref	p
	Test	Ref		
Beginning	3.26 (5.23)	2.85 (5.17)	1.14	0.078
Middle	3.18 (3.31)	3.03 (4.58)	1.05	0.033
End	3.26 (0.71)	2.92 (6.53)	1.12	0.054
Overall	3.23 (3.34)	2.93 (5.45)	1.10	0.002

Observations:

- Immediately before testing MDI canisters were heated in a 60°C water bath. This is inconsistent with the recommended clinical use of albuterol MDI's. Any procedure used for heating canisters may affect the particle size due to the accelerated evaporation of propellants at a temperature higher than the ambient. Therefore, the reviewer is not certain if these data has any relevance to the clinical use of albuterol MDI. However, during the November 21, 1996 tele-conference with the firm, OGD did not recommend a repetition of this test at the ambient temperature. Therefore the review is based on the data submitted previously.

- On an average the size of particles emitted by the test product was 10% greater than that of the reference product , and the difference between these products was statistically significant. However, in the absence of compendial criteria, and the acceptable *in vivo* bioequivalence and saftety of the test product, these data are acceptable.

V. Deposition of Emitted dose by Twin Impinger:

The apparatus used for this test was identical to the USP "Single Stage Impactor Apparatus 2" (USP, pp 1765). This apparatus is used to determine the fine particle size fraction of the dose discharged from MDI's through the inhalation actuator. When operated at an airflow rate of 60L/min, the lower impinger provides an aerodynamic particle cut off size of 6.4μM. Particles > 6.4μM are trapped in the upper chamber, and particles < 6.4μM are collected in the lower chamber.

The sponsor performed the test according to the USP. This test was performed using the lot #6403 of the test product and lot Z31383LS of the reference product, and it was accomplished within the expiry dates of these batches (vol 8.2 and 10.1). In this test primed MDI's were actuated into the impinger operated at an airflow rate of 60 ± 5 L/min. For each test 10 actuations (2 + 8, as recommended in the USP) were used. At the end of 10 actuations the apparatus was rinsed with methanol. Stage 1 washings included those from the mouthpiece to the round bottom flask. Stage 2 washings included those from the inner and outer areas of stage 2, inlet tube assembly and the conical flask. The washings were transferred to 50 mL volumetric flasks and diluted with methanol. The amount of albuterol in these samples was determined using . Procedures used for calculation of μg albuterol/actuation, % retained in stage 1 and stage 2 are given on pp 82 (volume 10.1).

The results of twin impinger analysis performed by the firm are given below. These data are based on previous submissions, no new data were submitted on January 6 and May 23, 1997.

	Albuterol Deposition (μg) Per Actuation			
	Test	Ref	Test/Ref	p
Upper Impingement Chamber	41.09 (5.31)	33.21 (9.79)	1.24	0.008
Lower Impingement Chamber	44.14 (3.90)	56.84 (4.82)	0.78	0.001
Respirable Fraction	0.54 (2.99)	0.57 (4.79)	0.95	0.064

Observation:

Deposition of albuterol at the upper and lower chambers was different between the test and the reference product, and these differences were statistically significant. It is noteworthy that unlike the reference product, the test product spray deposited approximately same amount of albuterol in the upper and lower chambers. However, in the absence of compendial criteria, and the acceptable *in vivo* bioequivalence and safety of the test product, these data are acceptable.

VII. Overall Comment

The sponsor has submitted *in vitro* performance data on several batches of the test product. As mentioned in the beginning of this review the Agency had requested the

sponsor at several occasions to perform additional *in vitro* testing . Some of the tests were requested at a stage when the batches used for the *in vivo* bioequivalence study (test: lot#6403 and the reference lot#Z31383LS) had already expired. The data submitted by the sponsor on expired batches were considered to be unacceptable.

Evaluation of some tests of the *in vitro* performance is based on three production lots of the test product and a new lot of the reference product. because requests for repetition of these tests by the Agency were made after expiration of test and reference products used for the bioequivalence study. Thus, data for uniformity of unit dose and two tests of particle size determination cascade impactor and Microscopy) are based on new lots. These data are indicative of comparable *in vitro* performance of the test and the reference product, and consistency among the three product lots of the test product.

VIII. Recommendations

1. The *in vitro* performance testing conducted by ALPHARMA (A.L. Laboratories) comparing its albuterol 90 μg per actuation Metered Dose Inhaler Lot# 8457 with the reference product, Ventolin^{R} 90 μg per actuation Metered Dose inhaler (lot #6ZP076) has been found to be acceptable to the Division of Bioequivalence. Furthermore, *in vitro* performance data submitted by ALPHARMA comparing three lots (#8457, #8671 and #8834) of its albuterol 90 μg per actuation Metered Dose Inhaler are acceptable to the Division of Bioequivalence.

   The *in vitro* testing should be incorporated into firm's manufacturing and stability programs. The test product should conform to USP test of content uniformity (USP chapter <905>). The Division of Bioequivalence recommends the following specifications as tentative based on data submitted by the firm:

MMAD:	microns
GSD	
Respirable fraction:	Not less than
Respirable dose:	Not less than

   Respirable fraction and respirable are based on drug

2. An *in vivo* bioequivalence study and a safety evaluation study conducted by this firm on the test product have been found to be acceptable to the Division of Bioequivalence (see DBE review dated April 29, 1997). The sponsor has

therefore met requirements of in vivo bioequivalence and in vitro performance testing on its albuterol metered dose inhaler, 90 μg/actuation.

Gur Jai Pal Singh, Ph.D.
Division of Bioequivalence
Review Branch II

RD INITIALED SNERURKAR
FT INITIALED SNERURKAR

CONCUR: _____ DATE 7/14/97
for Nicholas Fleischer, Ph.D.
Director
Division of Bioequivalence

GJP SINGH/ 6-18-97. 73-045I.O97

CC: ANDA# 73-045 (Original, duplicate), HFD-600 (Hare), HFD-130 (Jallen), HFD-655 (Nerurkar, Singh), Drug file, Division file.

ATTACHMENTS

Table 1A: Deposition of albuterol at various stages of the cascade imactor. (AL-LAB's 8457)

Total Deposition (15 Actuations)

	Beginning			Middle			End			Mean				%CV			
Stage	Can1	Can 2	Can 3	Can1	Can 2	Can 3	Can1	Can 2	Can 3	Total	Beg	Mid	End	Total	Beg	Mid	End
0	12.36	24.41	13.31	14.51	13.79	9.43	11.72	17.3	11.78	14.3	16.69	12.58	13.60	30.6	40.1	21.9	23.6
1	15.34	18.02	14.67	13.83	14.92	13.31	15.23	19.18	13.45	15.3	16.01	14.02	15.95	13.2	11.1	5.9	18.4
2	28.61	35.31	36.99	26.96	32.79	26.05	32.63	44.15	32.08	32.8	33.64	28.60	36.29	17.0	13.2	12.8	18.8
3	127.72	141.19	148	121.47	130.26	118.21	101.99	175.92	143.89	134	138.97	123.31	140.60	15.8	7.43	5.1	26.4
4	233.59	221.37	236.67	232.55	222.36	208.58	250.42	263.74	223.62	233	230.54	221.16	245.93	7.1	3.51	5.4	8.3
5	116.53	121.32	125.92	121.21	109.29	114.46	123.36	121.67	113.76	119	121.26	114.99	119.60	4.5	3.87	5.2	4.3
6	16.4	17.01	14.79	15.64	16.39	15.84	17.13	14.46	13.36	15.7	16.07	15.96	14.98	8.0	7.14	2.4	12.9
7	6.53	7.8	8.39	8.12	8.77	7.63	6.72	7.42	7.5	7.65	7.57	8.17	7.21	9.5	12.6	7.0	5.9
Filter	5.62	8.54	6.07	12.44	9.38	8.02	17.98	19.41	6.45	10.4	6.74	9.95	14.61	49.1	23.3	22.8	48.6
Valve Stem	42.12	43.54	70.53	42.48	43.73	96.14	41.43	41.24	96.71	57.5	52.06	60.78	59.79	41.5	30.7	50.4	53.5
Actuator	194.9	184.16	115.47	146.65	164.99	169.53	160.74	166.8	177.32	165	164.84	160.39	168.29	14.0	26.1	7.6	5.0
Ind. Port	1049.39	820.17	784.31	907.55	913.92	803.27	1069.23	1074.88	808.29	915	884.62	874.91	984.13	13.2	16.3	7.1	15.5
Total	1849.12	1642.85	1575.14	1663.4	1680.6	1590.47	1848.58	1966.18	1648.21	1718	1689.04	1644.82	1820.99	7.9	8.45	2.9	8.8

Deposition/ Actuation

	Beginning			Middle			End			Mean				%CV			
Stage	Can1	Can 2	Can 3	Can1	Can 2	Can 3	Can1	Can 2	Can 3	Total	Beg	Mid	End	Total	Beg	Mid	End
0	0.82	1.63	0.89	0.97	0.92	0.63	0.78	1.15	0.79	0.95	1.11	0.84	0.91	30.6	40.1	21.9	23.6
1	1.02	1.20	0.98	0.92	0.99	0.89	1.02	1.28	0.90	1.02	1.07	0.93	1.06	13.2	11.1	5.9	18.4
2	1.91	2.35	2.47	1.80	2.19	1.74	2.18	2.94	2.14	2.19	2.24	1.91	2.42	17.0	13.2	12.8	18.8
3	8.51	9.41	9.87	8.10	8.68	7.88	6.80	11.73	9.59	8.95	9.26	8.22	9.37	15.8	7.43	5.1	26.4
4	15.57	14.76	15.78	15.50	14.82	13.91	16.69	17.58	14.91	15.5	15.37	14.74	16.40	7.1	3.51	5.4	8.3
5	7.77	8.09	8.39	8.08	7.29	7.63	8.22	8.11	7.58	7.91	8.08	7.67	7.97	4.5	3.87	5.2	4.3
6	1.09	1.13	0.99	1.04	1.09	1.06	1.14	0.96	0.89	1.04	1.07	1.06	1.00	8.0	7.14	2.4	12.9
7	0.44	0.52	0.56	0.54	0.58	0.51	0.45	0.49	0.50	0.51	0.50	0.54	0.48	9.5	12.6	7.0	5.9
Filter	0.37	0.57	0.40	0.83	0.63	0.53	1.20	1.29	0.43	0.7	0.45	0.66	0.97	49.1	23.3	22.8	48.6
Valve Stem	2.81	2.90	4.70	2.83	2.92	6.41	2.76	2.75	6.45	3.84	3.47	4.05	3.99	41.5	30.7	50.4	53.5
Actuator	12.99	12.28	7.70	9.78	11.00	11.30	10.72	11.12	11.82	11	10.99	10.69	11.22	14.0	26.1	7.6	5.0
Ind.Port	69.96	54.68	52.29	60.50	60.93	53.55	71.28	71.66	53.89	61	58.97	58.33	65.61	13.2	16.3	7.1	15.5
Total	123.27	109.52	105.01	110.89	112.04	106.03	123.24	131.08	109.88	115	112.60	109.65	121.40	7.9	8.45	2.9	8.8

Table 1B: Deposition of albuterol at various stages of the cascade imactor. (Ventolin, 6ZP0756)

Total Deposition (15 Actuations)

	Beginning			Middle			End			Mean				%CV			
Stage	Can1	Can 2	Can 3	Can1	Can 2	Can 3	Can1	Can 2	Can 3	Total	Beg	Mid	End	Total	Beg	Mid	End
0	7.67	9.74	9.33	8.05	10.15	13.33	11.14	9.56	12.49	10.2	8.91	10.51	11.06	18.5	12.3	25.3	13.3
1	10.72	12.51	12.87	9.8	11.18	13.39	15.07	11.04	14.2	12.3	12.03	11.46	13.44	14.2	9.57	15.8	15.8
2	19.22	26.5	21.09	19.93	27.96	24.63	23.32	24.43	24.64	23.5	22.27	24.17	24.13	12.5	17	16.7	2.9
3	94.53	96.68	104.19	96.2	97.24	109.25	102.06	96.91	108.89	101	98.47	100.90	102.62	5.6	5.15	7.2	5.9
4	217.93	235.85	251.53	234.15	238.34	257.57	250.5	251.34	256.3	244	235.10	243.35	252.71	5.4	7.15	5.1	1.2
5	200.8	189.77	198.54	222.07	211.85	205.59	223.62	232.39	222.82	212	196.37	213.17	226.28	6.7	2.97	3.9	2.3
6	20.41	20.31	20.29	22.3	21.06	20.32	22.59	23.09	22.05	21.4	20.34	21.23	22.58	5.3	0.32	4.7	2.3
7	6.2	6.28	6.89	6.88	7.46	7.05	6.27	6.96	6.42	6.71	6.46	7.13	6.55	6.5	5.85	4.2	5.5
Filter	6.15	17.73	22.59	20.73	10.51	21.87	17.63	24.25	19.86	17.9	15.49	17.70	20.58	33.2	54.5	35.3	16.4
Valve Stem	9.15	14.68	13.93	13.03	11.55	12.79	9.4	14.47	12.38	12.4	12.59	12.46	12.08	16.3	23.8	6.4	21.1
Actuator	156.61	134.6	135.6	139.98	123.34	127.22	137.71	150.97	143.55	139	142.27	130.18	144.08	7.6	8.74	6.7	4.6
Ind. Port	725.38	739.08	801.97	716.34	758.9	767.26	699.36	716.34	796.06	747	755.48	747.50	737.25	4.9	5.41	3.7	7.0
Total	1474.77	1524.86	1629.29	1514.8	1555.85	1597.58	1461.73	1530.78	1627.03	1546	1542.97	1556.08	1539.85	4.0	5.11	2.7	5.4

Deposition/ Actuation

	Beginning			Middle			End			Mean				%CV			
Stage	Can1	Can 2	Can 3	Can1	Can 2	Can 3	Can1	Can 2	Can 3	Total	Beg	Mid	End	Total	Beg	Mid	End
0	0.51	0.65	0.62	0.54	0.68	0.89	0.74	0.64	0.83	0.68	0.59	0.70	0.74	18.5	12.3	25.3	13.3
1	0.71	0.83	0.86	0.65	0.75	0.89	1.00	0.74	0.95	0.82	0.80	0.76	0.90	14.2	9.57	15.8	15.8
2	1.28	1.77	1.41	1.33	1.86	1.64	1.55	1.63	1.64	1.57	1.48	1.61	1.61	12.5	17	16.7	2.9
3	6.30	6.45	6.95	6.41	6.48	7.28	6.80	6.46	7.26	6.71	6.56	6.73	6.84	5.6	5.15	7.2	5.9
4	14.53	15.72	16.77	15.61	15.89	17.17	16.70	16.76	17.09	16.2	15.67	16.22	16.85	5.4	7.15	5.1	1.2
5	13.39	12.65	13.24	14.80	14.12	13.71	14.91	15.49	14.85	14.1	13.09	14.21	15.09	6.7	2.97	3.9	2.3
6	1.36	1.35	1.35	1.49	1.40	1.35	1.51	1.54	1.47	1.43	1.36	1.42	1.51	5.3	0.32	4.7	2.3
7	0.41	0.42	0.46	0.46	0.50	0.47	0.42	0.46	0.43	0.45	0.43	0.48	0.44	6.5	5.85	4.2	5.5
Filter	0.41	1.18	1.51	1.38	0.70	1.46	1.18	1.62	1.32	1.19	1.03	1.18	1.37	33.2	54.5	35.3	16.4
Valve Stem	0.61	0.98	0.93	0.87	0.77	0.85	0.63	0.96	0.83	0.83	0.84	0.83	0.81	16.3	23.8	6.4	21.1
Actuator	10.44	8.97	9.04	9.33	8.22	8.48	9.18	10.06	9.57	9.26	9.48	8.68	9.61	7.6	8.74	6.7	4.6
Ind.Port	48.36	49.27	53.46	47.76	50.59	51.15	46.62	47.76	53.07	49.8	50.37	49.83	49.15	4.9	5.41	3.7	7.0
Total	98.32	101.66	108.62	100.99	103.72	106.51	97.45	102.05	108.47	103	102.86	103.74	102.66	4.0	5.11	2.7	5.4

Table 2: Deposition of albuterol at various stages of the cascade imactor (Test Product Lots)

Total Deposition (15 Actuations)

	lot # 8457			Lot #8671			Lot #8834			Mean			%CV		
Stage	Can1	Can 2	Can 3	Can1	Can 2	Can 3	Can1	Can 2	Can 3	8457	8671	8834	8457	8671	8834
0	12.36	24.41	13.31	16.96	13.44	9.5	10.35	9.72	12.74	16.69	13.30	10.94	40.1	28.1	14.6
1	15.34	18.02	14.67	17.13	14.52	12.03	11.02	9.33	11.02	16.01	14.56	10.46	11.1	17.5	9.3
2	28.61	35.31	36.99	39.52	29.97	27.67	21.23	21.81	20.75	33.64	32.39	21.26	13.2	19.4	2.5
3	127.72	141.19	148	130.26	120.61	110.76	102.81	110.92	102.41	138.97	120.54	105.38	7.43	8.1	4.6
4	233.59	221.37	236.67	210.66	195.65	194.75	220.42	222.97	215.88	230.54	200.35	219.76	3.51	4.5	1.6
5	116.53	121.32	125.92	154.89	146.07	151.25	163.75	145.38	157.02	121.26	150.74	155.38	3.87	2.9	6.0
6	16.4	17.01	14.79	23.12	21.88	23.83	19.35	18.48	20.34	16.07	22.94	19.39	7.14	4.3	4.8
7	6.53	7.8	8.39	9.25	9.33	9.59	12.1	7.62	7.87	7.57	9.39	9.20	12.6	1.9	27.4
Filler	5.62	8.54	6.07	20.71	6.14	2.98	8.41	9.18	10.11	6.74	9.94	9.23	23.3	95.1	9.2
Valve Stem	42.12	43.54	70.53	50.44	56.79	41.95	40.25	35.95	54.14	52.06	49.73	43.45	30.7	15.0	21.9
Actuator	194.9	184.16	115.47	206.84	151.43	159.87	174.45	150.66	231.59	164.84	172.71	185.57	26.1	17.3	22.4
Ind. Port	1049.39	820.17	784.31	973.58	849.46	972.54	835.97	803.03	850.08	884.62	931.86	829.69	16.3	7.7	2.9
Total	1849.12	1642.85	1575.14	1853.4	1615.29	1716.72	1620.09	1545.05	1693.96	1689.04	1728.46	1619.70	8.45	6.9	4.6

Deposition/ Actuation

	lot # 8457			Lot #8671			Lot #8834			Mean			%CV		
Stage	Can1	Can 2	Can 3	Can1	Can 2	Can 3	Can1	Can 2	Can 3	8457	8671	8834	8457	8671	8834
0	0.82	1.63	0.89	1.13	0.90	0.63	0.69	0.65	0.85	1.11	0.89	0.73	40.1	28.1	14.6
1	1.02	1.20	0.98	1.14	0.97	0.80	0.73	0.62	0.73	1.07	0.97	0.70	11.1	17.5	9.3
2	1.91	2.35	2.47	2.63	2.00	1.84	1.42	1.45	1.38	2.24	2.16	1.42	13.2	19.4	2.5
3	8.51	9.41	9.87	8.68	8.04	7.38	6.85	7.39	6.83	9.26	8.04	7.03	7.43	8.1	4.6
4	15.57	14.76	15.78	14.04	13.04	12.98	14.69	14.86	14.39	15.37	13.36	14.65	3.51	4.5	1.6
5	7.77	8.09	8.39	10.33	9.74	10.08	10.92	9.69	10.47	8.08	10.05	10.36	3.87	2.9	6.0
6	1.09	1.13	0.99	1.54	1.46	1.59	1.29	1.23	1.36	1.07	1.53	1.29	7.14	4.3	4.8
7	0.44	0.52	0.56	0.62	0.62	0.64	0.81	0.51	0.52	0.50	0.63	0.61	12.6	1.9	27.4
Filler	0.37	0.57	0.40	1.38	0.41	0.20	0.56	0.61	0.67	0.45	0.66	0.62	23.3	95.1	9.2
Valve Stem	2.81	2.90	4.70	3.36	3.79	2.80	2.68	2.40	3.61	3.47	3.32	2.90	30.7	15.0	21.9
Actuator	12.99	12.28	7.70	13.79	10.10	10.66	11.63	10.04	15.44	10.99	11.51	12.37	26.1	17.3	22.4
Ind.Port	69.96	54.68	52.29	64.91	56.63	64.84	55.73	53.54	56.67	58.97	62.12	55.31	16.3	7.7	2.9
Total	123.27	109.52	105.01	123.56	107.69	114.45	108.01	103.00	112.93	112.60	115.23	107.98	8.45	6.9	4.6

Table 3: MMAD and GSD values calculated from data submitted on January, 6, 1997 using the ECD values given by the firm and those used by the FDA's St. Louise laboratory.

A: Based on Firms' ECD values

MMAD

	TEST (8457)		REF		TEST/REF	*p*
	Mean	%CV	Mean	%CV		
Beg (11-25)	3.94	1.4	3.51	0.5	1.12	<0.05
Mid (76-90)	3.82	1.3	3.48	2.9	1.10	<0.05
End (186-200)	3.87	3.2	3.46	0.9	1.12	<0.05
Overall	3.88	2.3	3.48	1.7	1.11	<0.05

GSD

	TEST (8457)		REF		TEST/REF	*p*
	Mean	%CV	Mean	%CV		
Beg (11-25)	1.56	1.9	1.54	1.3	1.01	>0.05
Mid (76-90)	1.56	0.4	1.55	1.1	1.00	>0.05
End (186-200)	1.55	1.3	1.56	0.6	1.00	>0.05
Overall	1.56	1.2	1.55	1.0	1.00	>0.05

B: Based on the ECD values used by the FDA lab.

MMAD

	TEST (8457)		REF		TEST/REF	*p*
	Mean	%CV	Mean	%CV		
Beg (11-25)	2.52	2.0	2.19	0.7	1.15	<0.05
Mid (76-90)	2.57	1.5	2.31	3.4	1.11	<0.05
End (186-200)	2.60	3.7	2.30	1.1	1.13	<0.05
Overall	2.56	2.6	2.26	3.2	1.13	<0.05

GSD

	TEST (8457)		REF		TEST/REF	*p*
	Mean	%CV	Mean	%CV		
Beg (11-25)	1.74	2.7	1.72	1.5	1.01	>0.05
Mid (76-90)	1.65	0.6	1.64	1.1	1.01	>0.05
End (186-200)	1.64	1.9	1.65	0.7	0.99	>0.05
Overall	1.68	3.2	1.67	2.4	1.00	>0.05

Table 4: MMAD and GSD values for three lots of the test product calculated from data submitted on January, 6, 1997 using the ECD values given by the firm and those used by the FDA's St. Louise laboratory.

A: Based on Firms' ECD values

	MMAD			GSD		
	Lot #			Lot#		
	8457	8671	8834	8457	8671	8834
Can 1	3.89	3.71	3.57	1.54	1.63	1.55
Can 2	4.00	3.74	3.63	1.59	1.58	1.53
Can 3	3.92	3.65	3.61	1.54	1.56	1.56
Mean	3.94	3.70	3.60	1.56	1.59	1.55
%CV	1.4	1.2	0.8	1.9	2.3	1.0
8457/8671	1.06			0.98		
8457/8838	1.09			1.01		

B: Based on ECD values used by the FDA lab.

	MMAD			GSD		
	Lot #			Lot#		
	8457	8671	8834	8457	8671	8834
Can 1	2.48	2.35	2.23	1.71	1.63	1.73
Can 2	2.58	2.51	2.42	1.79	1.58	1.62
Can 3	2.51	2.44	2.40	1.72	1.56	1.65
Mean	2.52	2.43	2.35	1.74	1.59	1.67
%CV	2.0	3.3	4.4	2.5	2.3	3.4
8457/8671	1.04			1.09		
8457/8838	1.07			1.04		

Table 5: Respirable Dose and Respirable Fraction data based on January 6, 1997 amendment. ANDA #73-045

Drug < 5.8 microns

Respirable Dose

	TEST (8457)		REF		TEST/REF	p
	Mean	%CV	Mean	%CV		
Beg (11-25)	36.99	3.8	39.63	5.0	0.93	< 0.05
Middle (76-90)	34.81	4.0	41.84	2.6	0.83	< 0.05
End (186-200)	38.61	10.1	43.70	1.3	0.88	< 0.05
Overall	36.80	7.5	41.72	5.1	0.88	< 0.05

Respirable Fraction

	TEST (8457)		REF		TEST/REF	p
	Mean	%CV	Mean	%CV		
Beg (11-25)	0.38	11.3	0.43	0.9	0.88	> 0.05
Middle (76-90)	0.37	2.4	0.45	2.0	0.82	< 0.05
End (186-200)	0.37	8.1	0.46	3.3	0.80	< 0.05
Overall	0.37	7.4	0.45	3.5	0.82	< 0.05

Drug < 4.7 microns

Respirable Dose

	TEST (8457)		REF		TEST/REF	p
	Mean	%CV	Mean	%CV		
Beg (11-25)	34.74	3.3	38.15	5.1	0.91	> 0.05
Middle (76-90)	32.90	4.0	40.23	2.9	0.82	< 0.05
End (186-200)	36.20	9.6	42.09	1.2	0.86	< 0.05
Overall	34.61	6.9	40.16	5.2	0.86	< 0.05

Respirable Fraction

	TEST (8457)		REF		TEST/REF	p
	Mean	%CV	Mean	%CV		
Beg (11-25)	0.36	10.7	0.42	0.2	0.86	< 0.05
Middle (76-90)	0.35	2.8	0.43	2.7	0.81	< 0.05
End (186-200)	0.34	8.1	0.45	3.3	0.76	< 0.05
Overall	0.35	7.1	0.43	3.6	0.81	< 0.05

Drug <3.3 microns

Respirable Dose

	TEST (8457)		REF		TEST/REF	p
	Mean	%CV	Mean	%CV		
Beg (11-25)	25.48	2.2	31.58	5.2	0.81	< 0.05
Middle (76-90)	24.68	4.9	33.51	2.4	0.74	< 0.05
End (186-200)	26.82	8.2	35.25	1.7	0.76	< 0.05
Overall	25.66	6.2	33.45	5.5	0.77	< 0.05

Respirable Fraction

	TEST (8457)		REF		TEST/REF	p
	Mean	%CV	Mean	%CV		
Beg (11-25)	0.26	9.2	0.35	0.3	0.74	< 0.05
Middle (76-90)	0.26	3.9	0.36	3.3	0.72	< 0.05
End (186-200)	0.25	4.5	0.37	4.2	0.68	< 0.05
Overall	0.26	5.7	0.36	4.3	0.72	< 0.05

Table 6: Respirable Dose and Respirable Fraction data based on January 6, 1997 amendment. ANDA #73-045. Comparison of the three lots of the test product at the Begining testing stage

Respirable Dose

	LOT #									
	8457 (X)		8671 (Y)		8834 (Z)		X/Y	*(p)*	X/Z	*(p)*
	Mean	%CV	Mean	%CV	Mean	%CV				
Drug <5.8 microns	36.99	3.8	36.42	6.7	35.97	1.4	1.02	(>0.05)	1.03	(>0.05)
Drug <4.7 microns	34.74	3.3	34.26	5.9	34.56	1.4	1.01	(>0.05)	1.01	(>0.05)
Drug <3.3 microns	25.88	2.2	26.22	5.6	27.53	2.5	0.99	(>0.05)	0.94	(<0.05)

Respirable Fraction

	LOT #									
	8457 (X)		8671 (Y)		8834 (Z)		X/Y	*(p)*	X/Z	*(p)*
	Mean	%CV	Mean	%CV	Mean	%CV				
Drug <5.8 microns	0.38	11.3	0.36	4.7	0.39	2.0	1.06	(>0.05)	0.97	(>0.05)
Drug <4.7 microns	0.36	10.7	0.34	4.4	0.37	1.9	1.06	(>0.05)	0.97	(>0.05)
Drug <3.3 microns	0.26	9.2	0.26	3.3	0.30	1.6	1.00	(>0.05)	0.87	(>0.05)

Figure 1: Albuterol deposition profiles based on the cascade impactor data submitted on January 6, 1997 (ANDA #73-045)

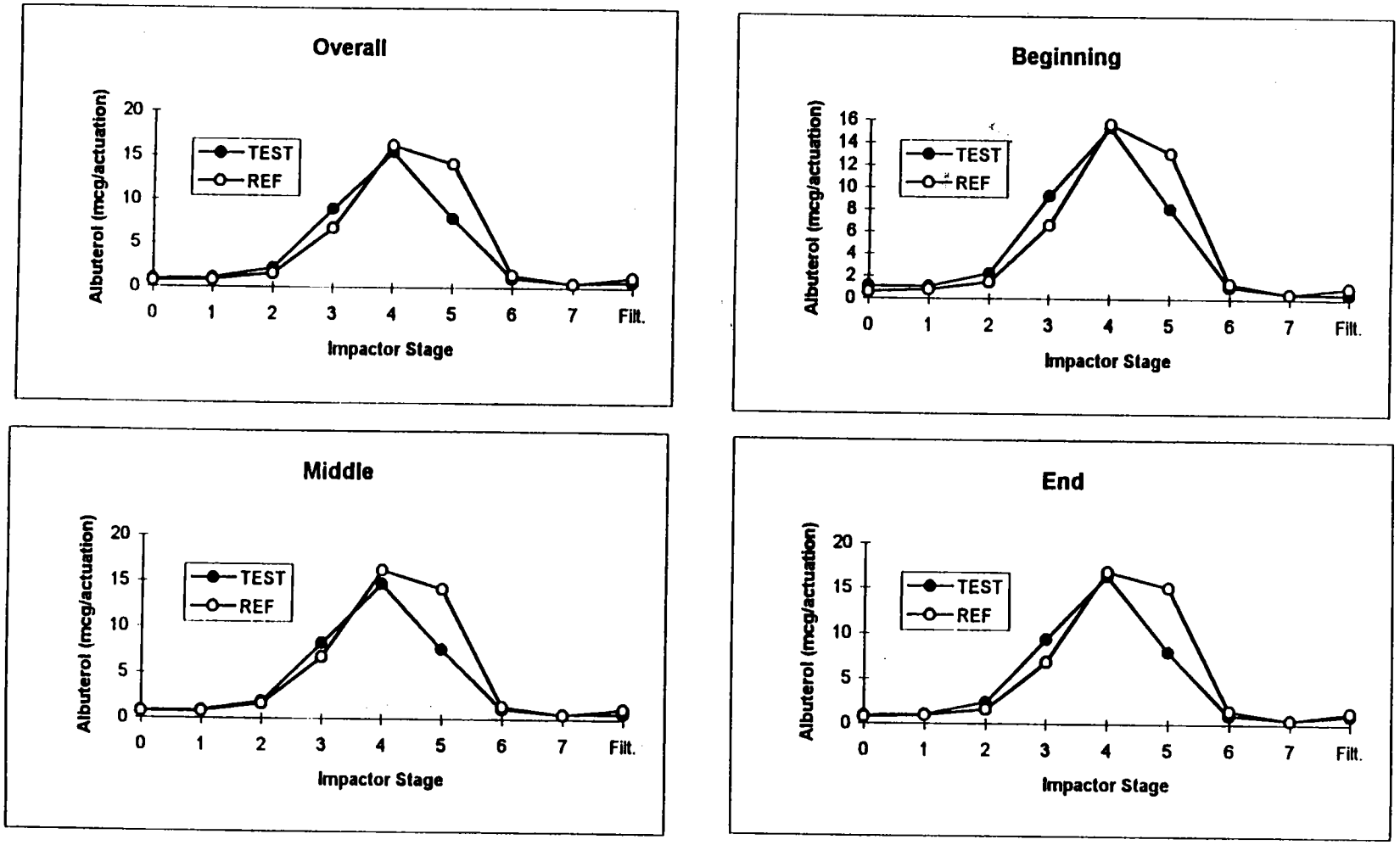

Figure 2: Albuterol deposition profiles for three lots of the test product based on data submitted on January 6, 1997 (ANDA #73-045)